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DEVELOPMENT OF SWIMMING AND RIGHTING REFLEXES IN FROG (*RANA GUENTHERI*): EFFECTS THEREON OF TRANSECTION OF CENTRAL NERVOUS SYSTEM BEFORE HATCHING

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(Received for publication September 25, 1940)

FOR THE past twenty years, the study of the behavior of the embryo of different species of vertebrates has been aimed mainly at tracing the stages of behavioral development and correlating them with those of the ontogeny of the central nervous system (CNS), the sensory apparatus and the effector organs. Except the experiments of Detwiler (1927, 1933) on the extirpation of the Mauthner's cells in relation to reflex activities in *Amblystoma* and the observations of Hooker and Nicholas (1930) on the reflexes of rat fetuses with the spinal cord severed at the dorsal segments, the surgical technique has seldom been resorted to in unravelling the nervous mechanisms underlying the development of behavior. The surgical technique in the hands of numerous neurophysiologists has given a large amount of knowledge conconcerning the functions of the different parts of the adult CNS of different vertebrates. This knowledge should form the foundation for the analysis of the nervous mechanisms underlying behavioral development. And it should be of considerable interest to compare the physiological effects of the same operation on the brain or the spinal cord in the adult with those in the embryo of the same species of *Vertebrata*. Such comparison may throw light on the physiology of the developing CNS.

With these purposes in view we have performed a series of experiments with the frog tadpoles to find out the effects of transection of the CNS at different levels at approximately the stage of gill-buds on the development of one aspect each of locomotion and posture, swimming and righting reflexes. The results of these experiments are here reported.

METHODS

Our experiments were carried out with the larvae of the frog *Rana güntheri*, the toad *Bufo bufo asiaticus*, and *Microhyla ornata*. Most of our results were obtained with tadpoles of the frog, and therefore our report will be restricted to this species only. However, we would like to mention that similar results to those presented in this paper were observed in the larvae of the toad and microhyla.

The frog eggs were collected from ponds near Kweilin in the three months from May to August of 1938, and 1940.

In each series of experiments, 50 or 100 embryos were used and equally divided into 5 groups: with the embryos in *group 1*, a lesion was made on the neural tube at such a level as would produce a complete severance of the cervical cord in the larvae; with those of *groups 2, 3 and 4*, at such a level as would produce in the larvae a complete transection of the CNS at the rostral border of the hindbrain, the midbrain and the interbrain respectively; while the embryos of *group 5* underwent no operation and served as controls. Altogether 10 such series were carried out.

The operations on the neural tube were performed with embryos about at the stage of gill-buds when they were still non-motile. Each embryo was shelled out of the egg, washed twice in water which had been previously boiled and cooled down to room temperature (*circa* 20°C.), subjected to operation on a sterilized slide under a dissecting microscope, with two sterilized needles as the cutting instruments, and thereafter transferred to a dish of boiled and cooled water. No anesthetic was used. The death rate due to operation was about 10 per cent. In the transection of the neural tube, a single section was insufficient to ensure the success of the intended operation, and it was necessary to tease out a strip of tissue after the incision was made. The success of our operations was about 60 per cent. In our preliminary experiments we employed a cautery for producing lesions on the neural tube, and found that without rigid and fine control of the temperature of the cautery it caused too extensive destruction of the tissues around the site of operation.

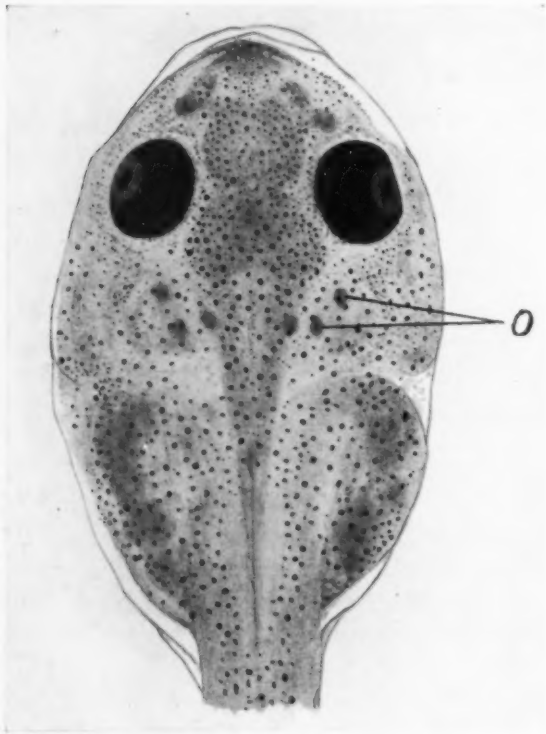

FIG. 1. Camera lucida drawing showing the outlines of the living brain of the larva of *Rana güntheri*. ×20 diameters. O = otoliths.

In some experiments carried out for the analysis of the results obtained, we amputated the tail and removed the labyrinths in a number of tadpoles. For labyrinthectomy we employed the following technique: A larva was immobilized by placing it in a mixture of water and ethyl alcohol for several minutes, and then laid on a sterilized slide under a dissecting microscope. The otoliths are visible as two dark spots on each side of the hindbrain (see Fig. 1). They and their adjacent tissues were easily destroyed with a needle. For amputation of the tail we simply incised it with a pair of scissors. No narcotic was used, and the wound was not closed, but care was taken to avoid the infliction of injury on the cloaca.

The larvae of *Rana güntheri*, when reared in a white procelain dish, are light orange in color, and the outlines of the brain remain visible to the naked eye and under the microscope for over a fortnight (see Fig. 1). Frequently we could see under the microscope the continual rostrad and caudad movements of a black particle in the fourth ventricle, indicating the existence of pulsation in the cerebrospinal fluid. Such enduring visibility of the outlines of the living brain proved a great advantage to us, working in a country at war where the abnormally high cost and the wellnigh inaccessibility of imported chemicals made it impossible for us to make preparations of the operated brain for microscopic examination. It enabled us to examine the operated living brain in each case as many times as necessary for determining the extent of the lesion made. In 10 cases these observations on the living larvae were controlled by dissections of brains after they were sacrificed and fixed in a 10 per cent aqueous solution of commercial formaldehyde for 3 or 4 days. The dissections done by Mr. H. T. Chang of this Institute who had not been informed about the sites of the lesions and the findings of behavioral observations confirmed the results of biopsy.

For tactile stimulation of the tadpole a horse hair securely tied onto a bamboo twig was used. This simple implement could be employed to put the larva on its back or side for a test of the presence of righting reflexes. For such a test we also adopted another method. We sucked a tadpole into the barrel of a medicine dropper, slowly turned the

dropper on the horizontal body axis of the tadpole therein and observed whether it would show any compensatory movements.

The body length of the tadpoles under experiment were measured to 0.1 mm. by means of a vernier caliper. The larva to be measured was placed on a slide and the caliper was applied to the larva underneath it. The accuracy of this procedure cannot be high. We controlled neither the food given to the tadpoles nor the temperature of their environment. Our measurements of body length served merely as a rough index of the growth of the tadpoles used.

Our observations of the behavior of the normal and operated larvae were continued up to 10 days after the gills were completely covered up by the operculum on both sides. By this time swimming and righting reflexes have already reached full development; we therefore deemed it unnecessary to follow it to the time of metamorphosis.

Results

Our results may be best described under the following headings.

A (1) *The normal development of swimming:* Coghill (1929) divided the development of swimming in *Amblystoma* into 5 stages: (i) the non-motile stage, (ii) the early flexure stage, (iii) the coil stage, (iv) the stage of the 'S' reaction and (v) the stage of aquatic locomotion. Youngstrom (1938) found similar stages in the ontogeny of aquatic locomotion in different species of Anura. According to our observations, *Rana güntheri* showed similar stages, except the coil stage. We have never found the embryo of this species of Anura in a tight coil.

However, we should like to point out that it may be better to divide the 5th stage of Coghill into 3 stages: namely, (v) the stage of translatory movements of the body, in which the larva performs the 'S' reactions in sufficiently quick successions to effect locomotion; (vi) the stage of the control of the direction of the translation of the body, in which it not only effects locomotion but also is able to avoid obstacles and to change the direction of motion whenever necessary; and (vii) the stage of the active maintenance of normal spatial orientation, in which it actively resists any attempt on the part of the investigator to put it on its back or side while it is swimming.

The last 2 stages were found to be easily affected by lesions on the CNS caudal to the diencephalon. The sixth stage was reached in *Rana güntheri* at a body length of 5 to 6 mm., and the seventh at a body length of about 9.5 mm. Here it should be mentioned that a tadpole of less than 9.5 mm. in body length always gained the normal orientation to the earth's gravitation field whenever it started to swim. This was found to be entirely due to the position of the center of gravity in the body, because any deformity of the body which displaced its mass center from its normal position would, as will be shown later, make these larvae swim on their back or side. At and after the seventh stage of the development of aquatic locomotion, a larva actively kept the dorsoventral axis of the body pointing to the center of the earth, although it could swim on its back or side when such a position of the body was required for securing food. Only after this stage was reached, could a tadpole be regarded as having acquired the ability of swimming, if the word 'swimming' is not taken to mean merely the translatory movements of the body.

We also wish to call attention to the fact that the tail is the only prime mover in the aquatic locomotion of the tadpole. We amputated tails of over 10 normal larvae, and found that a tailless larva was utterly powerless to change its position even a little on the bottom of the dish, not to mention to swim. The tail remained, indeed, the only motor organ in the early larval life.

(*2*) *The effects thereon of the transection of the CNS at different levels:* The complete severance of the cervical cord (section *1* in Fig. 2) prevented the operated larvae from reaching the final two stages of the development of aquatic locomotion. For 1 or 2 days after the operation, they showed no abnormality in behavior. Then it was noticed that the tail bent ventrad whenever it moved, presumably due to the exaggeration of the contraction of its flexors over that of its extensors. The spinal column then also showed ventrad flexion. The ventroflexion of the tail and the spinal column grew more and more marked every day and finally became a permanent posture. The body of the spinal tadpoles then assumed the form of a ring with a ventral opening of various sizes according as their spinal columns and tails were more or less ventrad flexed. As a consequence of this deformity, the center of gravity of the body was displaced to a more ventral position on its dorsoventral axis, and this displacement caused the larva to lie on its side while at rest. Whenever it attempted to move, it swam on its side in a circle: clockwise, in case it lay on its left side; and counter-clockwise, if on its right side. It could neither control the direction nor maintain normal spatial orientation while swimming.

In a number of larvae the transection of the spinal cord was unintentionally made caudad to the cervical region, and with 20 others the spinal cord was purposely severed at the dorsal or the lumbar segments. In all of them a permanently ventrad flexed tail resulted and the development of aquatic locomotion was arrested at the stage of translatory movements of the body. In order to prove that this arrest of the development of swimming is caused not by the deformation of the body but by the severance of the connections between the cord and the higher centers, we sought for a method of producing a ventrad curved tail without any injury to the CNS. By accident we found that such a tail was induced by several incisions suitably placed on the ventral side of the tail. This operation was performed on 10 normal larvae and observed that the ventrad curved tail hampered their swimming greatly but by no means prevented them from reaching the full development of aquatic locomotion. Moreover, we found that in one spinal tadpole the severed cervical cord became re-united 5 days after the operation leaving no visible trace of the original lesion either to the naked eye or under the microscope. This larva first showed the exaggeration of the flexor reflexes of the tail. Then the exaggeration of the flexor reflexes became decreased instead of increased in intensity, and finally disappeared. After this transient phase of accentuated flexor reflexes, the larva developed behaviorally just as a normal one.

The transection of the CNS at the caudal border of the midbrain (section *2* in Fig. 2) prevented the operated tadpoles from attaining the ability of maintaining normal spatial orientation during swimming. During the first day after the operation, the behavioral development did not deviate from its normal course. Then a gradual change in the posture of the tail occurred: it became permanently dorsiflexed. This is a phenomenon similar to the decerebrate rigidity of adult mammals, an over-reaction of the antigravity muscles. The extension of the tail varied widely in intensity from one decerebrated larva to another: from being barely recognizable to being so marked that the dorsiflexed tail made an angle of over 10 degrees with its base. Such extreme dorsiflexion of the tail displaced the mass center of the body to a more dorsal position on its dorsiventral axis. Consequently the tadpole lay partly on its side and partly on its back during rest, and swam on its back. It could, while swimming, alter its course in case this was necessary; but it never attempted to correct the *reversed* orientation to the earth's gravitation field. Even in those decerebrated larvae whose extension of the tail was not so marked, no active resistance was observed to the attempt on the part of the investigator to put it on its back or side while it was swimming.

The transection of the CNS was accidentally effected in a number of larvae at various places in the caudal two thirds of the hindbrain, and this operation was found to have the same effects on the development of aquatic locomotion as complete severance of the spinal cord. With five embryos the neural tube was transected at the level of or below the ear vesicles, and they all showed the same symptoms as the spinal tadpoles. All these observations justify the conclusion that the area in the hindbrain responsible for the control of aquatic locomotion is located in its rostral one third. From the structure of the medulla oblongata (Ariëns Kappers, Huber and Crosby, 1936), we may assume that this area corresponds either to the vestibular nuclei or to the reticular elements in the rostral one third of the hindbrain. There is no experimental evidence supporting either of these two alternatives.

On 10 decerebrated tadpoles we performed double labyrinthectomy. They all lost the control of the direction of aquatic locomotion, turning somersaults in every attempt at swimming. And they did not recover from this effect. These experiments certainly showed the importance of the impulses from the proprioceptors in the labyrinth for the control of the direction of swimming. In numerous normal and decerebrated larvae we found that the removal of both labyrinths without injury to the adjacent brain induced no exaggeration of flexor reflexes and no consequent deformation of the tail and the spinal column. This observation suggests that the impulses from the somaesthetic sense organs, including the proprioceptors in the musculature, play a large rôle in the control of reflex activities of the spinal cord by the motor center in the medulla oblongata.

The transection of the CNS rostrad to the rostral border of the midbrain (section *3* and *4* in Fig. 2) produced no effects whatsoever on the development of aquatic locomotion. The findings on the thalamic and mesencephalic

tadpoles, together with the changes observed in swimming after decerebration and severance of the spinal cord, located the highest center for aquatic locomotion of the tadpole in the mesencephalon. On account of the lack of facilities for making series sections of the operated larvae, we did not perform any experiment to further limit the location of this center. However, we may from many incidental observations venture the conjecture that it probably lies in the caudal half of the tegmentum. We found that the unintentional extirpation of the tectum did not arrest the full development of swimming, and that the accidental removal of the rostral half of the tegmentum together with the optic lobes also was without any effect.

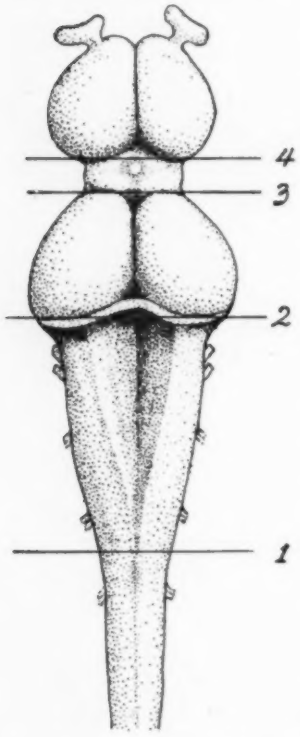

FIG. 2. Drawing of the dorsal view of the larval brain of *Rana güntheri* showing the four sections used in our experiments.

In this connection it should be mentioned that all the operations on the CNS did not retard the growth of the larvae, except the transection of the spinal cord which delayed it for 2 days. The tadpoles with the cervical cord severed were found to be difficult to rear. They invariably developed the communicating type of internal hydrocephalus. All the ventricles in the brain became greatly dilated; the puncture of the forebrain to release the accumulated cerebrospinal fluid brought about relief for at most 24 hours or even less. The loss of the ability of free swimming also gave them many difficulties in obtaining food. They survived the operation for less than 10 days.

B (1) The development of the righting reflexes: From the results presented in the preceding paragraphs it is evident that the righting reflexes developed rather late. They were observed to appear in the interval between the full growth of the gills and that of the operculum (body length from 6.5 to 9.5 mm.). The exact time of first appearance of these reflexes was very difficult to determine. The gills floating on both sides of the body acted as a kind of balancing organ, and mechanically assisted to a great extent the tadpole in keeping normal spatial orientation. When put on its back, it would right itself up with the assistance of the floating gills by any chance movement. When drawn into the barrel of a medicine dropper for observations on its compensatory movements to slow rotation of its body on the horizontal axis, it moved every time the gills came by chance into contact with the wall of the dropper; which was very difficult to avoid. However, repeated observations on a large number of larvae convinced us that they acquired the righting reflexes in the time interval stated above.

The time of first appearance of the righting reflexes was found to be later

than that of the coming into function of the proprioceptors in the labyrinth. With tadpoles of 6 mm. body length which had not as yet developed the righting reflexes, the ablation of both labyrinths produced the usual effects on locomotion: these larvae entirely lost the control of the direction of aquatic locomotion and turned somersaults whenever they attempted to swim.

(2) *The effects thereon of the transection of the CNS at different levels:* The transection of the CNS caudal to the rostral border of the hindbrain (sections *1* and *2* in Fig. 2) suppressed the development of the righting reflexes in the tadpoles, while the extirpation of the forebrain and the interbrain or of the telencephalon alone (sections *3* and *4* in Fig. 2) neither suppressed nor retarded the development of these reflexes. That the centre for the righting reflexes lies in the midbrain in the larva just as in the adult frog, found support in the following experiments. The destruction of the midbrain of a mesencephalic tadpole immediately abolished its ability of maintaining the normal orientation to the earth's gravitation field. Furthermore, we found that normal, thalamic and mesencephalic larvae of *Rana güntheri* could recover from the effects of double labyrinthectomy, provided that there was no concomitant injury to the hindbrain. On the extirpation of the mesencephalon in all these tadpoles the symptoms of double labyrinthectomy immediatedly returned, as did the loss of the righting reflexes and of the control of the direction of swimming. We have already stated that the decerebrated larvae never recovered from the effects of the removal of both labyrinths.

Discussion

From the work of Coghill (1914–1936, 1929) and Herrick (1937, 1938) on the correlation of the behavioral with the anatomical development in amblystoma, the following facts are known. The growth of the muscles and the somaesthetic sense organs precedes that of the spinal cord. In the non-motile stage the relative growth rate is the highest in the spinal and the post-facial region of the CNS, and from the stage of the early flexure to that of early swimming, in the post-facial region alone. The growth of the mesencephalon and the diencephalon begins to increase in rate at the 'S' reaction stage. No work along these lines has been carried out on the ontogeny of the CNS in *Rana*, and the observations by Coghill on the late stages of the development of swimming in *Amblystoma* are not comparable with our results on the frog. If it is justifiable to combine the facts discovered by Coghill and Herrick and our results, we may conclude that the maturation of the muscles and the somaesthetic sense organs and the spinal cord prepares for the advent of the stage of the translatory movements in the development of aquatic locomotion; that the full growth of the hindbrain antedates the stage of the control of the direction of swimming; and that the full development of the midbrain precedes the stage of the maintenance of normal spatial orientation during motion and rest. In short, each particular stage in the ontogeny of behavior follows maturation of the nervous mechansims con-

cerned, which is, in turn, preceded by that of the receptor and effector organs involved. This conclusion serves well as a generalization of the relations between the behavioral and the anatomical development in Amphibia.

Comparison of the normal development of swimming with the development after transection of the CNS at different levels in the frog brings out the following important fact. Although the severance of the spinal cord induces exaggeration of the flexor reflexes of the tail and decerebration enhances its extensor reflexes, yet no such phenomena have been encountered in the normal ontogeny of aquatic locomotion. From the fact that the maturation of the CNS proceeds *von unten nach oben*, we certainly expect to find them. The explanation of this fact is found in the following data discovered by Coghill and Herrick in Amblystoma. The accelerated growth of the medulla oblongata starts simultaneously with that of the spinal cord and outlasts it; while the development of the diencephalon and mesencephalon begins to increase in rate before the maturation of the hindbrain. The neurons in the higher centres send their axons caudad to the lower centres, before they have acquired functional connections with the incoming sensory and other tracts. Thus, the descending fibres from the neurons in the higher centres may, as suggested by Herrick (1938), exert some influences on the spinal centres at a time when the neurons have not yet assumed full function on account of the lack of the necessary connections with the incoming tracts. This seems quite possible, as we now know from the numerous investigations carried out in recent years on the electric activity of ganglionic centres (Davis, 1939) that the neurons are not merely passive tools in the hands of the receptor organs, but agents capable of spontaneous activity.

The findings of our experiments on the effects of transection of the CNS at different levels upon the development of aquatic locomotion and righting reflexes generally agree with the results of previous works on the changes in behavior after the same lesions on the brain and spinal cord in adult amphibians and mammals, including man. The clinical observations of Head and Riddoch (1917) established the fact that in men with injuries to the spinal cord, there is an exaggeration of the flexor reflexes and that this exaggeration disappears as soon as the patient recovers in cases where injuries have not caused permanent damages to the nervous tissue. This is just what we observed in our frog larvae with the spinal cord severed at different levels. The work of Sherrington (1915) on decerebrate rigidity proved that the transection of the brain at or adjacent to the caudal border of the mesencephalon induces an overreaction of the antigravity muscles. This also is just what we found in our decerebrated tadpoles. The investigations of Magnus (1924) demonstrated that the maintenance of normal body posture and normal orientation to the earth's gravitation field depends on the structural integrity of the midbrain. This, too, is just what we found in our frog tadpoles with the CNS transected at the rostral border of the mesencephalon.

However, the experiments on the larval brain and spinal cord, in comparison with those on the adult nervous system of the frog, show that the

lower centres of the growing CNS are more independent from the higher ones. In adult frogs, the transection of the CNS at the cervical region of the spinal cord, or at the rostral border of the hindbrain, or at the rostral boundary of the mesencephalon leaves them quite inactive, hardly showing any spontaneous activity. But the spinal, the decerebrated and the mesencephalic tadpoles are as spontaneously active as the thalamic and the normal ones (Wang and Lu, 1940). The higher centres seem gradually to acquire an ascendency over the spinal ones, finally having them entirely under control. The discovery and analysis of this process is an important problem in neurophysiology which still awaits experimental study.

Summary

1. The development of aquatic locomotion in *Rana güntheri* passes through the following stages: (i) the non-motile stage, (ii) the flexure stage, (iii) the stage of the 'S' reaction, (iv) the stage of translatory movements of the body, (v) the stage of the control of the direction of swimming, and (vi) the stage of the maintenance of normal orientation to the earth's gravitation field during motion and rest.

2. The last two stages are easily affected by transverse lesions made in the embryo on the central nervous system. The severance of the spinal cord arrests the development of swimming at the stage (iv); and after the transection of the brain at the caudal border of the mesencephalon, the development of aquatic locomotion does not reach beyond the stage (v). The removal of the forebrain and the interbrain, or of the telencephalon alone has no effect whatsoever on the ontogeny of swimming.

3. The righting reflexes appear in the stage (vi) of the development of swimming; and the transection of the central nervous system at any level caudad to the rostral border of the hindbrain prevents the operated larvae from acquiring these postural reflexes. With tadpoles of 6 mm. body length which have not yet developed the righting reflexes, the removal of both labyrinths produced its usual effect on locomotion in making them lose the control of the direction of swimming.

4. The transection of the spinal cord induces in the larvae an exaggeration of the flexor reflexes of the tail, and consequently causes it to be permanently ventroflexed; while decerebration produces an accentuation of the extensor reflexes of the tail, and consequently makes it permanently extended. Such effects are absent after the transection of the central nervous system rostrad to the rostral border of the midbrain.

5. The normal and mesencephalic larvae can recover from the effects of double labyrinthectomy, if there is no concomitant injury to the hindbrain. On the transection of the brain at the caudal boundary of the mesencephalon immediately return the symptoms of the extirpation of both labyrinths. The decerebrated tadpoles do not recover from the effects of double labyrinthectomy.

6. The spinal, decerebrated and mesencephalic tadpoles are as spon-

taneously active as the diencephalic and normal ones. This is entirely contrary to the findings on the adult frogs.

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THERMOCOAGULATION OF MOTOR CORTEX EXCLUSIVE OF ITS SIXTH LAYER*

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DESTRUCTION of all layers of a circumscribed cortical area by thermocoagulation (at 80°C. for 5 sec.) completely abolishes the electrocorticogram (ECG) in the entire region of thermocoagulation. If one of the two electrodes is placed 0.5 mm. outside the boundary of coagulation a normal ECG is obtained. These two findings demonstrate first, the ECG originates in the cortex, and second, its source is highly localized. After partial thermocoagulation (T.C.) of a cortical area, the surviving deeper layers, even in the acute experiment, exhibit electrical activity. This activity, however, is not undisturbed. In such an acute experiment the destroyed superficial laminae are still present, preventing the direct lead-off from the layers underneath; furthermore, the coagulation products are acid in reaction, and their diffusion into immediately subjacent cortical layers reduces the electrical activity of the latter.[5]

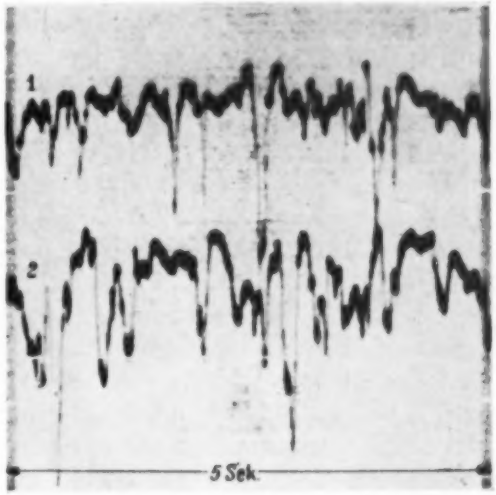

FIG. 1. Electrocorticograms from A.4 region of a macaque's brain (Dial-narcosis). Record 1 from an area reduced to two inner layers by local thermocoagulation (chronic experiment, 70°C—3 sec.), record 2 from normal A.4. No essential difference between the two ECGs. Same amplification in the two records (After Dusser de Barenne and McCulloch).

In the *chronic* T.C. experiment, on the other hand, the superficial, killed cell-layers have been resorbed completely,[2] and it is thus possible to obtain from such a "reduced" cortex a true picture of the electrical potentials of the remaining layers. Elimination of the external laminae of the "motor" cortex, in the chronic thermocoagulation experiment, with preservation of the large and giant pyramidal cells as well as those of the polymorphic variety,[6] results in no essential change of the ECG (Fig. 1).

It remained, therefore, to investigate the electrical function of the "motor" cortex reduced to its innermost, or polymorphic layer. In the solution of this problem the following chronic experiments were undertaken.

* The data in this paper are taken from the thesis presented by J. P. Murphy in partial fulfilment of the requirements for the degree of Doctor of Medicine, Yale University, 1939.

EXPERIMENTS

Experiment 1.— Thermocoagulation of motor cortex with destruction of all but polymorphic ganglion-cell layer. Persistent but eventually remitting paresis of contralateral upper extremity. Marked reduction in electrical activity of coagulated area two months later.

On November 9, 1938, under ether narcosis, the right precentral and post central motor cortex of *Macaca mulatta* was exposed. The entire precentral arm region was thermocoagulated at 75°C. for 6 sec. The procedure was finished in 1 hr. and 45 min. While the animal was still on the operating table and asleep, marked diminution in muscle tone was noted in the left upper extremity. When seen in his cage 2 hr. and 30 min. later the monkey was alert and feeding. Severe paresis was evident in the arm, particularly in its distal portion. The hand was used little, and not at all for finer movements. It was often placed in abnormal positions on the floor. The grip was extremely weak and movements of defense were executed with definite ataxia. A slight improvement in the motility of the paretic limb was noted on the first post-operative day; this became more definite one day later. At the end of the first week gross movements involving the proximal joints were being undertaken.

Two months were allowed to elapse before electrical records were taken. There was now no difference between the two arms in motion and muscle-tone. On January 9, 1939, the animal received 0.5 cc. of Dial (Ciba) per kg. body-weight, half intraperitoneally and half intramuscularly, and was re-explored. The cerebral dura, although not thickened, was adherent to the region of thermocoagulation. The pachymeninx was not removed in order that the electrical activity of the two symmetrical A.4 areas could be recorded under similar conditions. Bipolar stigmatic Ag-AgCl electrodes were placed 2.5 mm. apart on the surfaces of the areas under investigation, and electrical records from the cortex taken with a Westinghouse oscillograph (Fig. 2).

After the taking of ECGs, the position of the two electrodes on the thermocoagulated site was marked by means of a narrow, shallow incision in the dura. The animal was then killed with an overdose of ether. The brain was

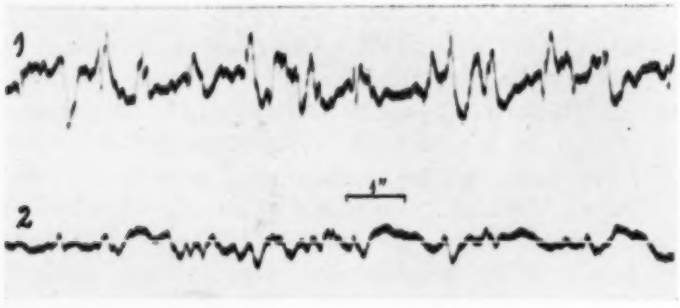

FIG. 2. Electrocorticogram from A.4 region of a macaque's brain (Dial-narcosis) taken *through dura*. Record 1 is taken from left A.4 (normal), record 2 from right A.4 reduced to inner layer of polymorphic cells (chronic thermocoagulation experiment, 75°C—5 sec.) Same amplification in the two records. Speed of paper: 10 cm. = 7 sec.

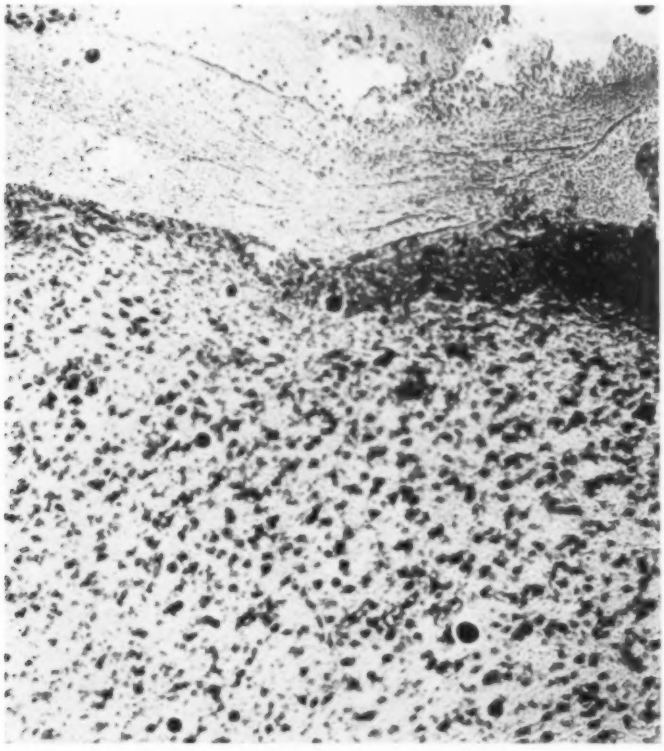

FIG. 3. A demonstrative section of the area under the electrodes. Beneath the dura lies a narrow band of fibroblasts and glia. Immediately underneath this may be seen undamaged polymorphic ganglion cells. The large and giant pyramidal cells of the fifth layer are gone.

removed and placed in 95 per cent alcohol for microscopic serial sectioning and staining by means of the Nissl technique.

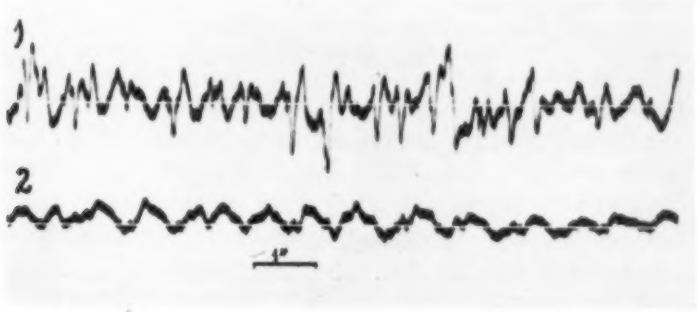

FIG. 4. Electrocorticograms from A.4 regions of a macaque's brain (Dial-narcosis), taken *directly from cortex*. Record 1 taken from left A.4 (normal), record 2 from right A.4 reduced to inner layer of polymorphic cells (chronic thermocoagulation experiment, 71°C—7 sec.). Same amplification in the two records.

Experiment 2.—Thermocoagulation of area A.4 sparing polymorphic ganglion-cell lamina alone. Long-lasting motor deficit in arm of opposite side. ECG recorded from operated site after interval of two months reveals extremly low frequency and amplitude of potentials, as in Experiment 1.

The second animal was operated upon on November 14, 1938. The right sensorimotor cortex was exposed under ether narcosis and laminar thermocoagulation of A.4 was effected at 71°C. for 7 sec. The dura and scalp were closed in the usual manner. Six hours later failure to use the left arm or hand

FIG. 5. A representative section of the area underlying the electrodes. On the surface of the resorbed cortex lies a layer of clotted blood, immediately beneath there is fibroblast proliferation together with gliosis. No cells of the large or giant pyramidal types are visible. Below the glia remain intact cells of the sixth, or polymorphic layer.

for picking up food or in defense movements was observed. The extremity was employed in an awkward fashion, however, in walking and climbing. The fingers, hand, and arm frequently remained in abnormal positions. It was possible to abduct the limb far laterally without any correction of posture and without appreciable resistance. The hand was often placed on the dorsum when used for support. The next day, food was being taken only with the right hand. No grasping power could be detected in the left hand when a bar was placed in the palm, but there were gross movements in the proximal joints of the arm. Motor impairment had cleared markedly two weeks later.

After a two-month interval, at the end of which there was no observable

difference between the two upper extremities, the animal received Dial as outlined in the first experiment, and the field of previous operation was re-exposed. The dura could be removed with ease and without damage to the area of thermocoagulation. The left sensorimotor arm region was uncovered and stripped of its dura as well. Electrodes were placed at a distance of 2.5 mm. from each other on the surfaces of homologous gyri, and electrical activity was then recorded (Fig. 4).

Following the marking of the position of the two electrodes on the thermocoagulated cortex by means of a very fine linear incision, the animal was killed with ether, and the brain was fixed in 95 per cent alcohol for serial sectioning and Nissl staining (Fig. 5).

All of the sections from the region of coagulation were carefully studied. In some few of the sections the resorption of the destroyed cortex included polymorphic cells, their place being taken by glia. However, these "glial clefts" were narrower than the diameter of the electrode-bulb.

Discussion

It is evident from a consideration of Fig. 1 as contrasted with Fig. 2 and 4 that there is a marked dissimilarity between the electrocorticogram obtained from the "motor" cortex reduced to its two inner layers, and that taken from a similar cortical region in which nothing but the last, or polymorphic cell-layer remains. In the former, the ECG is indistinguishable from that of the normal area 4—in the latter, there is manifest a striking reduction in frequency and amplitude of electrical potentials. The difference between the two sets of experiments is only attributable to the fact that in the latter the layer of large and giant pyramidal cells has been eliminated.

Another salient point of contrast is that while the animal whose "motor" cortex has been destroyed only to the extent of the four outer layers exhibits at most a very slight and transitory motor impairment,[1] that in which thermocoagulation of the "motor" area has included the layer of large and giant pyramidal cells evidences typical and long-lasting motor deficit, as may be seen in the protocols outlined above.

Conclusions

Significant diminution of the electrocorticogram and pronounced, long-lasting motor deficit are produced by laminar thermocoagulation of the precentral "motor" cortex, when the coagulation is extensive enough to include the large and giant pyramidal cells, but not layer VI, in area A.4 and the homologous fifth layer in the other precentral arm areas (A.4-s and A.6).

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TRANSMISSION OF IMPULSES THROUGH THE BURDACH NUCLEUS

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THE SEQUENCE of potential changes that takes place after the stimulation of dorsal root fibers, as recorded with electrodes placed on the segment of the dorsum of the spinal cord corresponding to the root level, is characterized by a primary spike, followed by a slow negative and a positive intermediary potential (Gasser and Graham, 1933). This potential sequence, steadily decreasing in size, can be recorded several centimeters above the level of entrance of the afferent volley (Hughes and Gasser, 1934a); and with needle electrodes in the proper tract of the dorsal column the primary spike can be followed up to the medulla (Hursh, 1940). The purpose of the present investigation has been to follow the transition of the impulses from the primary neurons to the secondary neurons of the nuclei of Goll and Burdach. For the sake of convenience the afferent fiber system connected with the Burdach nucleus has been used more or less exclusively, but supplementary information has been obtained from the Goll system as well.

A few anatomical facts of interest may be recalled in this connection. According to Cajal (1909) collaterals of the long ascending branches of the dorsal root fibers are given off in the greatest number to the grey matter of the spinal cord over three or four segments above the root, and then to the nuclei of Goll and Burdach in the medulla. In the latter the connections are made with the cells that form the arcuate fibers, without the intervention of interneurons within the nuclei. Thus a straight relay occurs in sufficient anatomical isolation from the adjacent complex synaptic systems to provide a favorable situation in which relays of this sort may be studied physiologically without undue interference arising from simultaneous activity in the neighborhood. The dorsal root fibers from the cervical and upper thoracic segments terminate in the cuneate (Burdach) nucleus and partly in the external cuneate nucleus of Clarke-Monakow (Ferraro and Barrera, 1935), while fibers from the lumbar and sacral segments terminate in the gracilis (Goll) nucleus. The synaptically transmitted impulses of the Goll and Burdach nuclei cross the midline in the internal arcuate fibers and pass to the thalamic nuclei in the medial lemniscus.

METHODS

Cats, decerebrated or under Dial narcosis (0.5 cc./kg.), were used exclusively. The spinal cord was usually exposed down to the lower cervical segments. The posterior part of the skull was opened and the cerebellum removed, thus exposing the floor of the IVth ventricle as well as the anterior part of the Goll and Burdach nuclei. For stimulation, the ulnar, median, and radial nerves of the forelimb were used, either separately or in combination. In the hindleg stimulating electrodes were applied to the sciatic nerve trunk. To record the potential changes in the spinal cord and the medulla a small Ag-AgCl ball electrode was placed on the dorsal surface, with an indifferent electrode on inactive tissue. For studying

electrical activities within the nervous structures a steel needle having a tip diameter of approximately 50μ and insulated to its tip was used. The customary stimulating device and differential amplifier system were employed.

The rectal temperature of the cats was kept between 38° and 39.5°C. In several of the cases the exposed part of the central nervous system was covered with oil.

Results

The characteristic potential changes described by Gasser and Graham (1933) as obtained in the lumbar region after a dorsal root stimulation are also produced in the lowest cervical segments when a stimulating shock is ap-

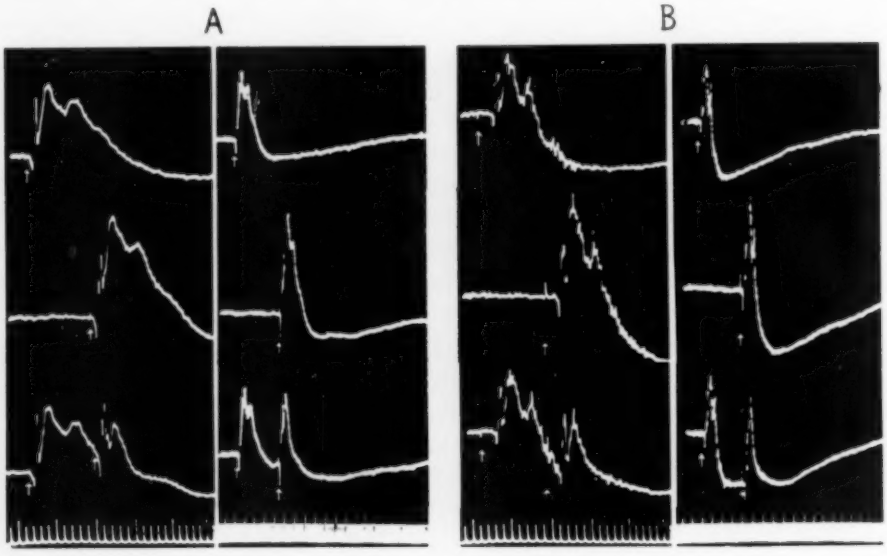


FIG. 1. Two stimulating shocks applied to the ulnar nerve; the first shock of submaximal strength, the second supramaximal. Records taken with surface lead, in column *A* at C_7, in column *B* at the cuneate nucleus. Shock intervals 9 and 20 msec. Shock artifacts marked with arrows. Time, 1 and 5 msec. Cat under Dial narcosis. Upward deflection in these and all subsequent records indicates negativity at the "active" lead.

plied to the ulnar, median, or radial nerve of the forelimb. Figure 1A shows these familiar features, with the primary spike followed by a prolonged negative wave, on the descending phase of which a second negative elevation is commonly seen. This elevation corresponds to the "first negative complex" of Hughes and Gasser (1934a). The duration of the negative and positive waves respectively, as well as the way in which they are modified by a preceding volley, is also in correspondence with the generally known facts about the potentials in the lumbar part of the spinal cord (Hughes and Gasser, 1934b). As the primary volley proceeds towards the cuneate nucleus, the same potential sequence, though decreased in size, is reproduced in the higher segments. When the nucleus itself is reached, the form of the action potential still follows the same general contour (Fig. 1B) but some differences appear. All the potentials are larger, particularly the positive potential, and the negative potential following the primary spike is shorter.

The primary spike. The usual distance of conduction from the stimulated point of the forelimb nerve to the nucleus was 9–10 cm., necessitating a conduction time of 1.5–2.0 msec. Shocks to the nerve strong enough to stimulate all the alpha fibers produced maximal tract spikes; and as the duration of the spike at the medullary level was only about 1.0 msec., the indication is that a fairly homogeneous set of fibers is involved.

The post-primary negative potential at the cuneate nucleus. Measurements of the duration of the post-primary negative wave are made inexact by the shifting of the base line occasioned by the concomitantly recorded positive potential. But 5 msec. may be taken as a fair average value. About 3 msec. after the arrival of the primary spike a second negative elevation is commonly recorded on the falling slope of the first elevation.

In connection with the negative potential following the primary spike, the question must be raised as to whether all the potential is generated in the nucleus in sequence to the impulses that are recorded in the primary spike, or whether a part of it may be set up by impulses already relayed through cord neurons, and recorded, therefore, as a part of the post-primary cord potential. Against the latter idea is the consideration that, while there are known to be numerous intrinsic fibers in the dorsal columns of the spinal cord (Tower, 1937), none of them is known to make connection with the nucleus. Evidence against the idea is also obtained in a physiological experiment. If the relaying of impulses at any segment of the cord is blocked, thereby eliminating the local production of potentials, a lead from the segment will reveal only the potentials in the fibers that are passing by the segment in the tracts. Blocking can be accomplished by injecting small amounts of distilled water, 0.1 to 0.2 cc., into the grey matter beneath the dorsal column. Figure 2 shows the potential changes recorded at levels 1 cm. apart at approximately the following cervical segments: C_6–C_7 (record 1), C_5 (2), C_3–C_4 (3), C_2 (4), C_1 (5), and at the cuneate nucleus (6). An injection was made into the grey matter at the level of C_3–C_4. As a result it is seen that, while at all other levels the negative and positive post-primary potentials retain their normal form, at the affected segment the potential is limited to the primary spike and a small negative potential separated from it by 2–3 msec. (record 3). From this result it follows that the potentials segmentally recorded are, outside of the exception indicated, locally produced and that they do not represent relayed activity passing toward anterior parts of the nervous system.

The second exception can be identified both by the time lag behind the primary spike and in other ways with the dorsal column relay (Hursh, 1940), which is associated with the dorsal root reflex described by Toennies (1938).

While evidence is lacking for the intervention of relayed impulses other than the dorsal column relay of Hursh, in the setting up of the post-primary negative potential of the nucleus, the idea cannot be dismissed unless it can be shown that the duration of the potential can otherwise be accounted for. In all, a duration of 5 msec. must be explained. The arrival of the dorsal root relay about 3 msec. after the start of the primary spike could account for the

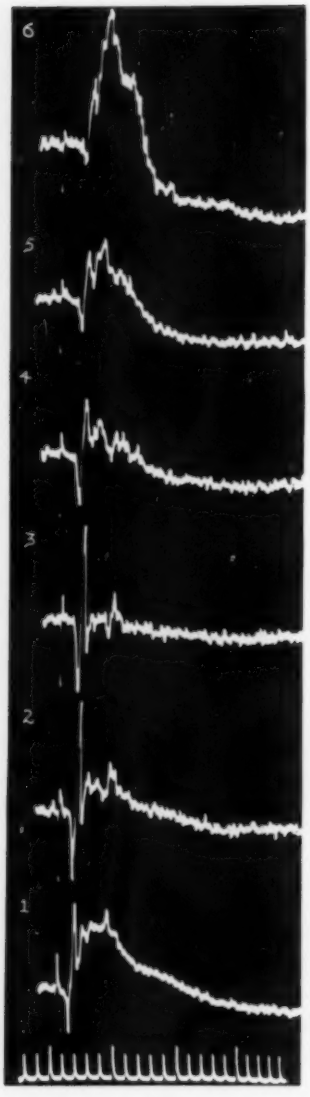


FIG. 2. Stimulation of ulnar nerve. Records taken with surface lead at each of the following levels which were 1 cm. apart: *1* at C_6–C_7; *2* at C_5; *3* at C_3–C_4; *4* at C_2; *5* at C_1; *6* at the cuneate nucleus. An injection of 0.2 cc. of distilled water into the grey matter was made previous to records at level of record *3*. Note absence of intermediary potentials. The primary spike and the dorsal column relay persist at the level of injection. Shock artifact visible in all records. Time, 1 and 5 msec. Cat under Dial narcosis.

production of the later part of the potential Hence it is upon the first part of the potential that attention must be focused. Only two times can be brought into the argument: the synaptic delay and the duration of the potential in active secondary neurons. The minimal synaptic delay at the cuneate nucleus was found to have a constant value of 0.6 msec., which is in good agreement with synaptic delays elsewhere (Lorente de Nó, 1935 and 1938; Renshaw, 1940). If in addition there are longer delays, they cannot be measured, as the start of the relayed potential would be obscured by the potentials set up after the minimal interval. However, it might be safe to assume a variation equivalent to that seen in other situations (Lorente de Nó, 1938; Renshaw, 1940), in which case 1.0 msec. could be taken as the maximum.

About the duration of the potential in the nerve cells there is less certainty, because of the difficulty of interpreting the form of the potentials led from active tissue surrounded by a conducting medium. Measurement of the potential recorded by Lorente de Nó (1939) when an antidromic volley was fired into a pool of motoneurons indicates a duration of 1 msec.; and that 1 msec. may be taken as a fair figure for the neurons of the cuneate nucleus is indicated in some of the records published in the present paper. For instance, the duration of the activity in a highly synchronized group of neurons recorded in Fig. 8 is about 1 msec. Earlier in the paper the duration of the primary spike as recorded at the nuclear level was given as 1.0 msec.; but again this value is only approximate, because of the triphasic character of the record.

If we consider the primary volley coming to the Burdach nucleus to last 1.0 msec. and the maximal synaptic delay to be 1.0 msec., then the last of the potentials in the secondary neurons would start 1.5 msec. after the beginning of the primary volley. If to this time we add 1 msec. for the duration of the potential of the secondary neurons, the total is 2.5 msec., which is slightly

under the 3 msec. period, the filling of which the problem demanded. On the assumption that the missing 0.5 msec. could be made up from the uncertainties in the basic data, it would be possible to account for the post-primary negative potential in the Burdach nucleus on the basis of a two-neuron chain aided by the dorsal column relay; but the reservations about the adequacy of the accounting are so serious that the question of whether there may be some, as yet unidentified, relayed impulses coming into the nucleus should be left open.

Activity in the medial lemniscus. At practically the same time at which the post-primary negative potential starts in the nucleus (0.6 msec.), the first impulses can be recorded with a needle electrode in the medial lemniscus. In obtaining the action potential from the medial lemniscus fibers it has been found convenient to injure the fibers at the point of recording by pushing the needle through the bundle and then withdrawing it for about 1 mm. Thereby the small triphasic deflections that would be obtained from intact fibers are converted into large positive deflections. The form of the potential as led in this way is shown in Fig. 3. Listed in order, beginning at the top, the figure shows records obtained at the following levels: C_2, C_1, cuneate nucleus, medial lemniscus after decussation, and medial lemniscus 1 cm. cephalad.

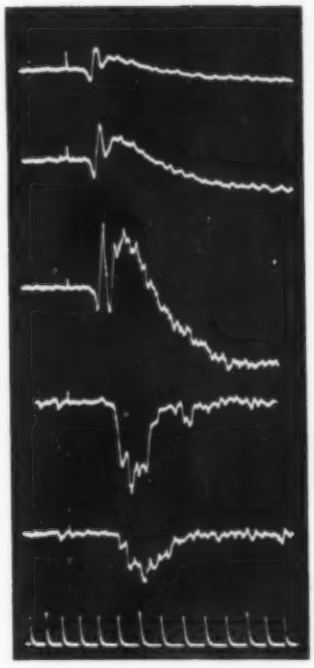


FIG. 3. Stimulation of ulnar nerve. Conduction distance between each record 1 cm. Beginning from above the records are taken at the following levels: C_2, C_1, cuneate nucleus, medial lemniscus, and medial lemniscus 1 cm. further cephalad. Note positive deflections in these and subsequent medial lemniscus records due to recording from "killed ends." Time, 1 and 5 msec. Cat under Dial narcosis.

Above the nucleus, as would be expected, the primary spike is no longer visible. By measuring from the shock artifact and allowing 0.17 msec. for conduction, it can be shown that the discharge into the lemniscus fibers starts at the beginning of the post-primary negative potential in the nucleus. The discharge lasts as long as the nuclear negativity persists. (In the figure the duration of the latter is not easily determined because of the displacement occasioned by the positive potential.) It will also be noted that 3 msec. after the start of the lemniscus potential there is a discrete wave marking the appearance of the discharge from the nucleus set up by the dorsal column relay. In the lemniscus there is no activity correlating with the positive potential recorded at the cuneate nucleus.

The positive potential. The activity that supplies the large positive deflection in surface leads from the nucleus appears for the most part not to be directly connected with the nucleus itself. Support for this statement is found in the fact that the negative and positive deflections can be dissociated, and also in the findings obtained with an exploring needle.

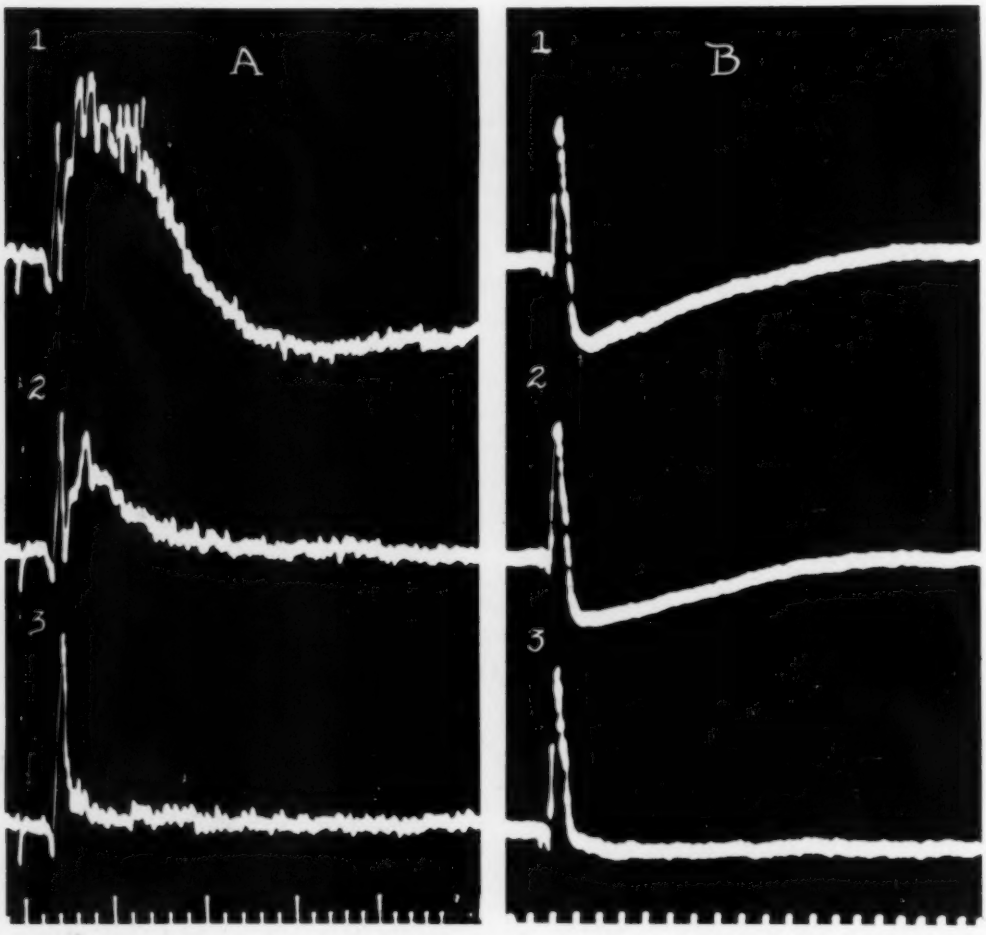


FIG. 4. Stimulation of median nerve and recording with surface lead at the cuneate nucleus, *A* and *B*, from two different experiments. Uppermost records (A_1 and B_1) taken with cats in normal conditions. In column *A* records taken at different stages of circulatory asphyxia after heart was stabbed. In column *B* the records *2* and *3* were taken at two early stages of progressive respiratory asphyxia. Time in *A*, 1 and 5 msec.; in *B*, 5 msec. Cats under Dial narcosis.

Injection of distilled water at a level 3–4 mm. below the surface of the medulla may reduce the size of the positive potential, without affecting that of the negative potential. Experimentally, however, it was found impossible to obliterate the positive potential entirely without affecting the negative potential.

Dissociation of the negative and positive components can also be effected by asphyxia, to which the positive component is the more susceptible (Fig. 4). The records in column A are from an experiment in which the heart was stabbed, but they are also typical for experiments in which respiratory asphyxia was produced. Record 1 was taken before the circulation was stopped, and 2 and 3 during successive stages of asphyxia. In 2 the positive

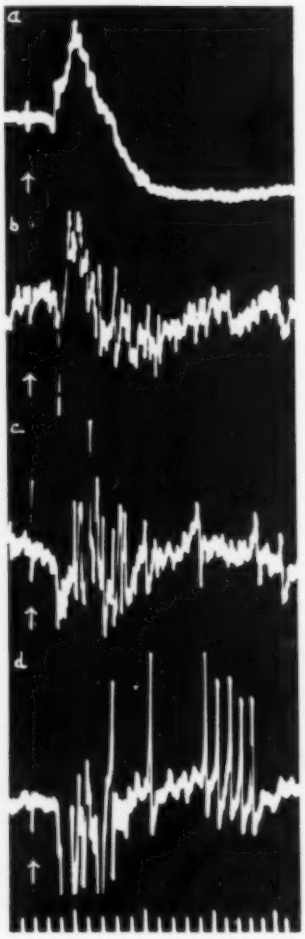


FIG. 5. Stimulation of median nerve. Records obtained with a needle electrode: *a*, on the surface of the cuneate nucleus; *b*, *c*, and *d*, at depths of 0.5, 1.0, and 2.0 mm. in the nuclear region. Amplification for records *b*, *c*, and *d* approximately the same as for *a*. Time, 1 and 5 msec. Cat under Dial narcosis.

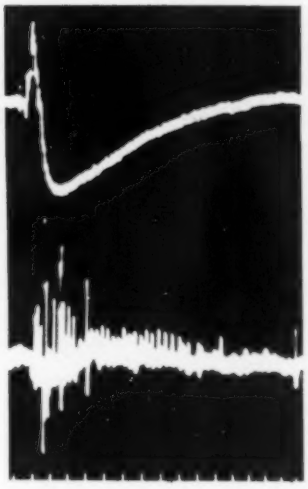
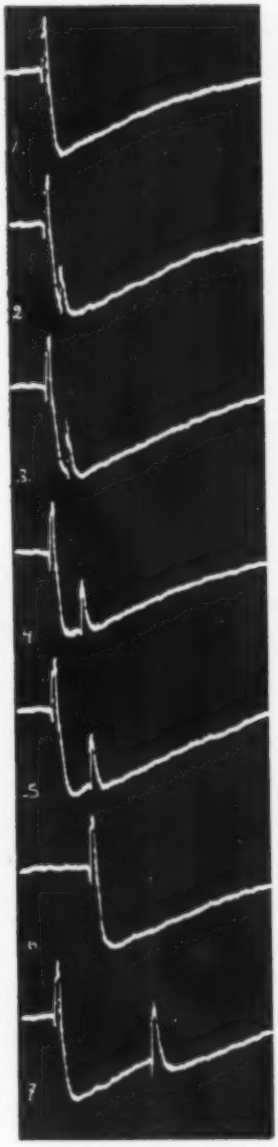


FIG. 6. Same experiment as in Fig. 5 but surface record (upper) obtained with ordinary surface lead; the lower record was taken with the needle in new position at a depth of 2+ mm. Time, 5 msec.

FIG. 7. Stimulation of ulnar nerve with two maximal shocks (6 times threshold) at different shock intervals. Recording with surface lead at the cuneate nucleus. Record *1* control of conditioning volley; *6* control of testing volley. Note completed recovery of negative post-primary potential in record *4* at a shock interval of 15 msec. Time, 5 msec. Cat under Dial narcosis (0.4 cc. per kg.).



wave has disappeared, but the negative wave has also decreased in size. At a late stage of the asphyxia (3) only the primary spike remains. In column B it is shown that the positive wave may almost completely disappear before any change in the size of the negative wave has taken place. The effect is reversible, and full recovery was obtained during the following period of normal breathing.

The findings obtained with an exploring needle are illustrated in Fig. 5, which shows leads obtained at three different depths in comparison with a surface lead. The first change observed as the needle penetrates the pia is the breaking down of the negative component into spikes (b). As the needle is pushed further, the spikes become more prominent and all signs of a positive wave are lost (c). When the needle goes beneath the nucleus at the depth of 2 mm., the spikes are recorded with their phases reversed and a late series of large spikes appears (d). The latter are also recorded at deeper levels. This prolonged discharge evoked by a single afferent volley, which may last for 50 msec. or more, is correlatable with the time course of the positive wave on the surface (Fig. 6). There can be little doubt that it is the activation of the reticular substance in this region that gives the prolonged discharge. This interpretation is supported by the facts that the reticular formation appears at a depth of about 1.5–2 mm. from the surface (Winkler and Potter), and that similar activities in corresponding regions are recorded after an afferent sciatic volley.

In view of the foregoing sets of evidence the positive potential recorded from the surface of the nucleus must be largely attributed to activity outside of the nucleus, and to this extent it is an artifact as far as the nucleus is concerned. As such it would obscure any positivity developed intrinsically in the nucleus; consequently it should not be assumed that no positivity of this sort is developed in the nucleus.

Response to two stimuli applied to the same nerve. The effect of a conditioning volley on the spinal cord potentials is well known from previous work (Gasser and Graham, 1933; Hughes and Gasser, 1934b; Hughes *et al.*, 1937). That an obvious similarity exists between the reaction of the cuneate nucleus and the spinal cord is shown in Fig. 1.

The recovery of the negative potential at the cuneate nucleus has been determined in a series of experiments using two supramaximal shocks, 6 to 7 times threshold. In several cases it has been found that the negative wave has regained its full size at shock intervals of not more than 15 to 20 msec. (Fig. 7). But there is considerable variation from preparation to preparation as to the time required for full recovery. It is often necessary to increase the shock interval to 50 msec. or even more, until the negative wave has recovered completely. The cause of this variability has remained obscure, but it has not been possible to correlate it with the size of the positive wave.

The effects of a conditioning volley at short intervals before the testing volley are shown in Fig. 8. When the interval is shorter than 2 msec. the properties of the primary axons become a determining factor (Gasser and Graham, 1933). Thus at an interval of 1 msec. (see figure) the conduction time of the second primary spike is prolonged and the spike is reduced in size. At this interval the second primary spike still, however, clearly elicits an immediately following short-lasting negative wave, which is found superimposed on the negative wave produced by the conditioning volley. Although reduced in size, a negative wave of this sort can be found at any shock in-

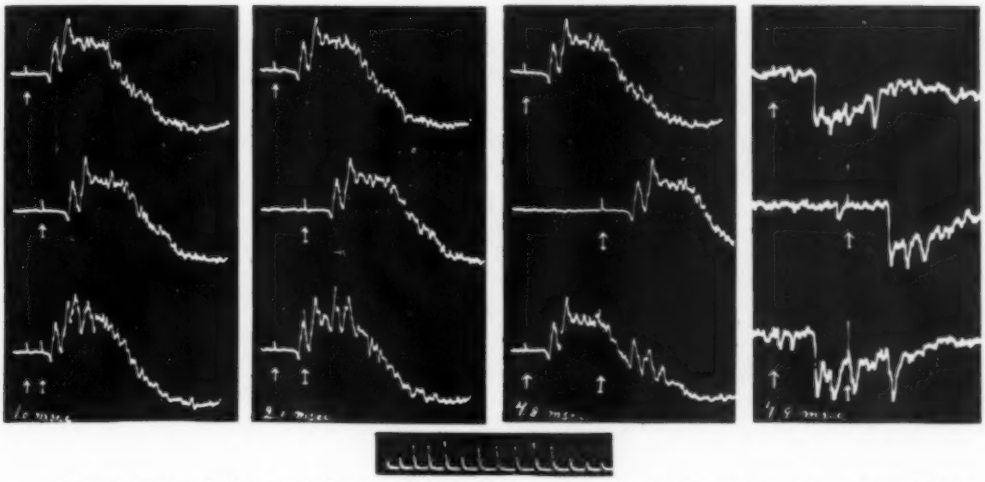


FIG. 8. Stimulation of ulnar nerve with two maximal shocks (7 times threshold). Recording with surface lead at the cuneate nucleus at shock intervals of 1.0, 2.1, and 4.8 msec., and with a needle electrode in the medial lemniscus at a shock interval of 4.9 msec. Shock artifacts marked with arrows. Time, 1 and 5 msec. Decerebrated cat.

terval at which a second primary spike can be evoked. The duration of the wave added by the second shock to the pre-existing negativity is about 1 msec., and it is interesting to note that this duration remains constant until the shock interval is increased to about 5 msec., *i.e.* the duration of the unconditioned negative wave as determined at the baseline level. The height of the conditioned negative wave never exceeds the height of the corresponding part of the unconditioned response and the time interval between the crests of the primary spike and the negative wave remains at its unconditioned value, *i.e.* approximately 0.6 msec. This finding is shown in Fig. 8 at shock intervals of 2.1 and 4.8 msec. (It may be noted that at the shock interval of 4.8 msec. the second primary spike is decreased in size, presumably due to occlusion by the dorsal column relay of the conditioning volley.) After 5 msec. the duration of the conditioned response begins to be prolonged, and the subsequent course of the recovery is as has been described above.

The records in the last column of Fig. 8 were ob-

FIG. 9. Same experiment as in Fig. 7. Usual surface picture taken at the cuneate nucleus in uppermost record; below, similar recording but tetanic stimulation at a frequency of approximately 150 per sec. The lower most record shows the discharge in the medial lemniscus at the same stimulating frequency. Shock artifact visible only in the medial lemiscus record. Time, 1 and 5 msec.

tained from the medial lemniscus (approximately 1 cm. post-synaptic conduction) at a shock interval of 4.9 msec. When a comparison is made of these records with those taken at a corresponding shock interval from the surface of the cuneate nucleus, it is obvious that the two have similar features. In the medial lemniscus the response to the second shock is also shortened to a duration of about 1 msec. and its size, as compared to the unconditioned response, is somewhat reduced. A similar correspondence between the nuclear and the lemniscus responses occurs at other shock intervals as well, and it is still maintained during a tetanus. In Fig. 9 the two upper records were obtained with a surface lead from the nuclear region, and the lower record with a needle electrode in the medial lemniscus. The frequency of the tetanus in both cases was about 150 per sec. The negative wave pro-

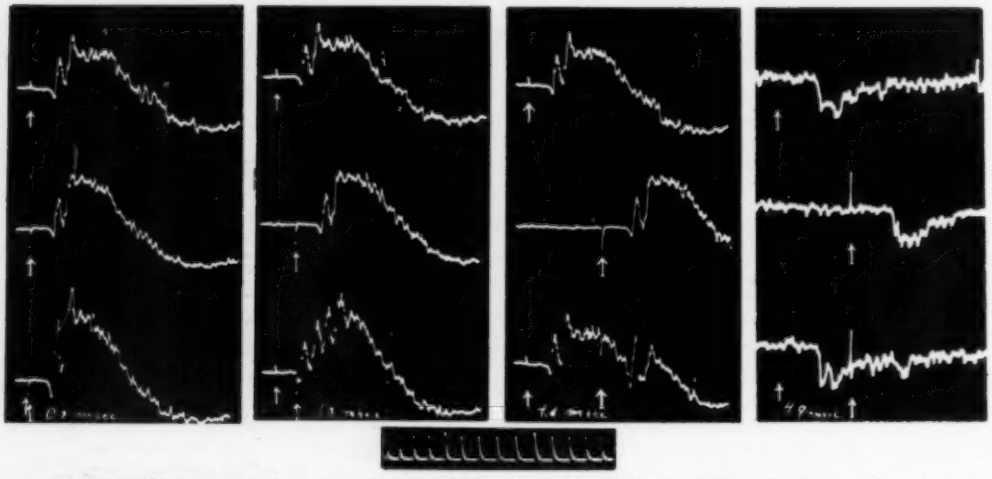


FIG. 10. Same experiment as in Fig. 8. Similar recording and identical amplification as well as speed of sweep. The two shocks delivered to different nerves (ulnar and median nerves) at intervals of 0.1, 1.3, and 4.8 msec., and at 4.9 msec. in the record from the medial lemniscus.

duced by the second shock is somewhat reduced, but it will be seen that a further reduction does not occur during succeeding shocks. The same statement applies to the discharge in the medial lemniscus.

All activity relating to the dorsal column relay, whether it is recorded in the nucleus or in the lemniscus, is inhibited for a long period by a conditioning volley, as would be expected from the description by Hursh of the conditioning of the relay itself.

Response to two stimuli applied to different nerves (Fig. 10). When the two shocks are delivered at approximate simultaneity (0.1 msec. shock interval), a complete summation of the primary spikes is obtained, but the size of the negative post-primary potential recorded at the nucleus is smaller than the sum of the individually obtained responses. Most of the deficit occurs in the late part of the wave, and there is in fact a considerable addition of the potentials appearing during the first millisecond after the primary spike. A

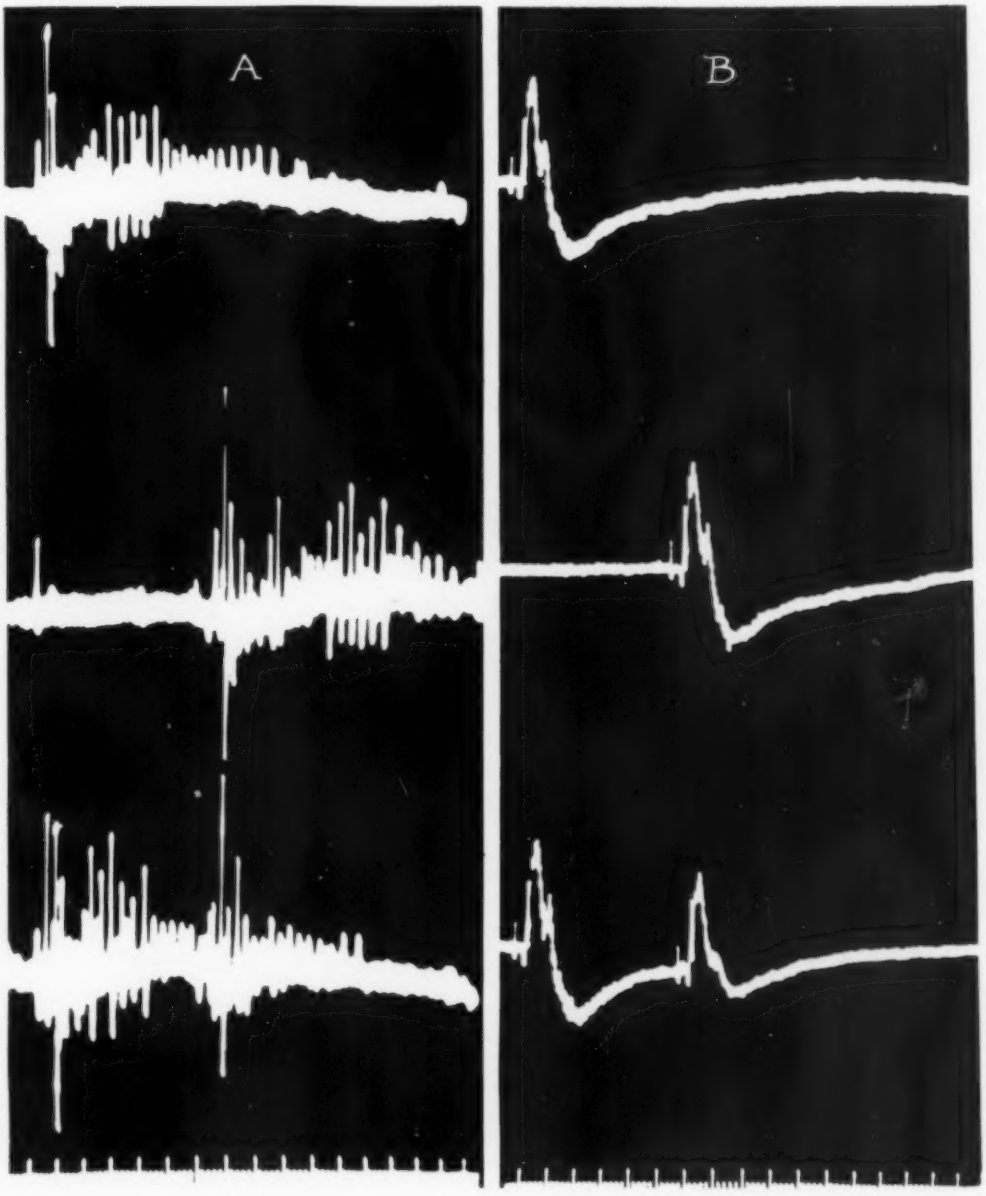


FIG. 11. Stimulation of median nerve with two maximal shocks at an interval of 30 msec. In column *A* the records were taken with a needle electrode inserted to a depth of 2 mm. below the surface of the cuneate nucleus. The records show, beginning from above: conditioning volley alone; testing volley alone; conditioning volley and testing volley 30 msec. apart. Corresponding surface records are in column *B*. Time, 5 msec. Cat under Dial narcosis.

similar addition occurs when the volleys are separated by short intervals. After 4 to 5 msec. the later part of the conditioned negative wave starts to regain its size. Recovery is usually complete at intervals of 15 to 20 msec.,

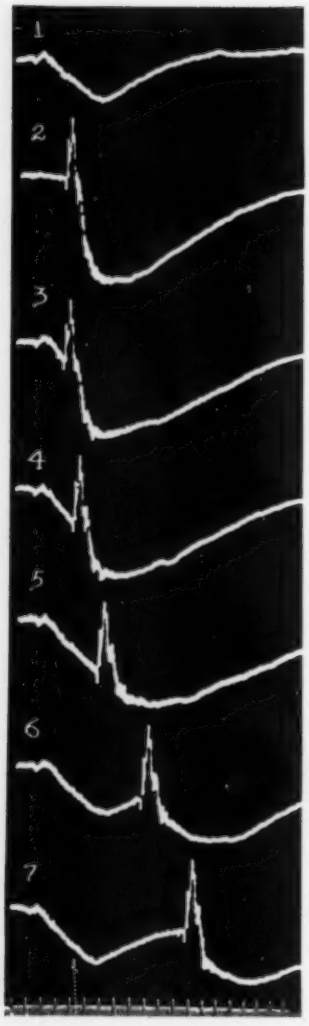


FIG. 12. Stimulation of sciatic and median nerves (ipsilateral). The potential changes are recorded with a surface lead at the cuneate nucleus. Record *1*, sciatic volley alone; *2*, median volley alone; *3–7*, sciatic volley succeeded by the median volley at progressively increasing time intervals. Time, 1 and 5 msec. Cat under Dial narcosis.

but longer intervals, up to 50 msec., may sometimes be required. These effects on the negative wave elicited by a conditioning volley are again reflected in the medial lemniscus response by corresponding changes. It may be noted that neither response attains a supermaximal size, nor is a reduction of the latency demonstrable at any shock interval.

In another series of experiments the first of two shocks was applied to the sciatic nerve and the second to the median nerve of the homolateral forelimb. The usual records were taken with surface leads at the Burdach nucleus, a location which is obviously not favorable for recording any potential changes arising in the Goll nucleus. Figure 12 shows the effect of the sciatic volley alone (1) and succeeded at different intervals by the median volley (3, 4, 5, 6, 7); and the effect of the median volley alone (2). It is obvious that the size of the negative post-primary potential produced by the median volley is little, if at all, affected by a preceding sciatic volley. On the other hand, the positive wave is greatly reduced. This reduction is greatest if the median volley arrives at a time when the positive wave produced by the sciatic volley has reached its maximum.

Positive wave as affected by a conditioning volley. Irrespective of whether the two shocks are applied to the same or to different nerves of the forelimb the amount of positivity that can be added by a second volley at a certain shock interval is practically the same. This increase of positivity becomes appreciable at shock intervals of about 2 msec. Successively longer shock intervals are associated with a progressive increase of the positivity added by the second volley (Fig. 7).

The last spike discharge obtained with a needle electrode at a depth of about 2 mm. below the cuneate nucleus is also affected by a conditioning volley. In Fig. 11, column A, it is seen that the effect of the second volley is reduced in duration. As the occlusion of the positive potential recorded from the surface of the nucleus (column B) parallels the deficit in the conditioned train of spikes, additional support is given to the interpretation of the positive wave as the potential effect at the surface of the cord of activity in the reticular substance.

Discussion

The outstanding feature of the cuneate nucleus is its powerful one-to-one relay. A volley entering the resting nucleus, after a minimal synapse time of 0.6 msec., produces a burst of activity in the cuneate neurons, which is reenforced about 3.0 msec. later by the arrival of the relayed discharges in the dorsal columns described by Hursh. The total activity lasts about 5 msec. and is recorded by an electrode on the surface of the nucleus as a negative wave. Throughout the continuation of the wave relayed impulses pass anteriorly in the lemniscus fibers.

The powerful part of the relay is confined to the early period of the discharge. Transmission is then so effective that if two shocks are applied to a peripheral nerve at any interval sufficiently long to produce a second response in the nerve fibers, the second volley on arriving at the nucleus will set up a short burst of impulses in the tract (lasting about 1.0 msec.). Up to intervals of 5 msec. the relayed impulses are confined to this short burst, then the latter begins to be followed by other impulses. As the interval is increased, the discharge is prolonged and augmented in its later portions; and resting-control dimensions are attained after 15–50 msec., depending upon the conditions.

From this brief description it is apparent that in addition to direct and powerful relays through the nucleus there are also pathways that are easily conditioned. Part of these pathways can be accounted for through the dorsal column relay. The latter takes fully as long to recover from previous activity as does the discharge in the lemniscus. Hence in so far as the dorsal column relay contributes to the lemniscus discharge, the latter cannot reach full value before the former. All of the easily conditioned pathways cannot be explained in this way, however; because there is a conditioned deficit in the discharge during the first three milliseconds before the dorsal column relay arrives. How one would explain the conditioning depends on how one explains the production of the potential itself during this period. If, contrary to any knowledge about them, one postulates other prenuclear relays, the explanation would be in the pattern obtaining for the dorsal column relay. If, on the other hand, one holds that the activity is all set up by the primary tract spike, then one has to assume that some of the branches of these fibers make less powerful connections than do others, and that a higher degree of recovery is necessary for the weaker connections to have threshold stimulating value than for the stronger.

Summary

Following a single shock applied to a nerve of the forelimb there passes through the dorsal column to the nucleus of Burdach a volley of primary impulses succeeded after about 3 msec. by the dorsal column relay of Hursh. These impulses produce in the nucleus (surface lead) a post-primary negative potential lasting about 5 msec. During the course of this potential, impulses are discharged into the lemniscus.

Conditioned transmission through the nucleus has the following properties: The refractory period at the synapse is not longer than that of the primary axons. Transmission after the second of two volleys at intervals less than 5 msec. is limited to a short burst of spikes (lasting ca. 1.0 msec.) following the second primary volley by a synapse time of 0.6 msec. Addition of the later, more inhibitable, portion of the transmitted impulses starts at intervals of 5 msec. and restoration is complete at 15 to 50 msec. Thus the transmission of a tetanus through the nucleus is essentially one-to-one conduction between primary neurons and neurons of the lemniscus fibers.

A positive wave lasting about 100 msec., recorded at the surface of the nucleus, is correlated with activity in the underlying reticular substance.

I wish to express my sincerest appreciation and thanks to Dr. Herbert S. Gasser for his encouraging interest and criticism during the course of this investigation.

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INFLUENCE OF DISCHARGE OF MOTONEURONS UPON EXCITATION OF NEIGHBORING MOTONEURONS

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Introduction

Some spinal motoneurons are equipped with recurrent collaterals which arise from the axon near its origin and terminate in association with other neurons of the ventral horn (cf. Cajal, 1909). An impulse that sweeps over the motor axon must also invade its collaterals. Does it then affect the excitability of the neurons in association with which the collaterals terminate? Müller (1835) could produce no muscular contractions by stimulating the central end of a cut motor root. Others have likewise failed to find evidence that an antidromic volley produces either a centrifugal discharge in motor axons or activity in other nerve tracts (Mislawski, 1895; Bernstein, 1898; Eccles, 1931). In the absence of known excitatory effects it has been suggested that impulses in recurrent collaterals might lead to inhibition of the activity in the neurons to which they pass (Graham Brown, 1914; Gesell, 1940). The collaterals would then be an important part of the mechanism for reciprocal innervation. Forbes and his collaborators (1933) put the suggestion of Graham Brown to a careful experimental test. They found that a contralaterally evoked reflex discharge into the tibial nerve is not conditioned by antidromic volleys arriving at the cord in the motor axons of the peroneal nerve.

The present experiments show that the antidromic activation of certain groups of motoneurons does condition the reflex discharges of other motoneurons. The conditioning effect is often inhibitory. It is then neither preceded by facilitation nor delayed; inhibition is present when the antidromic volley reaches the cord approximately simultaneously with an afferent volley which fires the testing motoneurons directly after a single synaptic delay. The inhibition must then be caused by events occurring during the synaptic delay at the motoneurons—a period of only 0.9 msec. or less (Lorente de Nó, 1938; Renshaw, 1940). The conditioning volley cannot have fired either the tested motoneurons or premotor interneurons in time for the refractoriness (subnormality) which follows activity to mediate the response deficit (cf. Gasser, 1937a, b; Lorente de Nó, 1936).

In a discussion of this phenomenon it would be misleading to focus attention only upon the possible role of recurrent collaterals. It is not necessary to infer from the early onset of inhibition that a specific inhibitory action is produced by the arrival of impulses at the synapses made by the recurrent collaterals with other neurons. As Grundfest (1940) has pointed out, an alternative explanation for findings of this sort is suggested by the fact that

activity in axons can alter the excitability of adjacent, structurally independent axons (Adrian, 1930; Jasper and Monnier, 1938; Arvanitaki, 1940b; Katz and Schmitt, 1940). Evidence has also been supplied to show that activity in neurons in the central nervous system can affect the discharges of adjacent neurons in the absence of synaptic associations (Barron and Matthews, 1935; Gerard and Libet, 1940).

In the experiments about to be described it has been necessary to activate the conditioning motoneurons antidromically. The results have a more general significance, however, for it may be supposed that in any experiment synaptic excitation of the same motor cells would have produced similar effects (Sherrington, 1900).

METHODS

The preparations were cats, either decerebrated or under light barbiturate anesthesia (Dial; Nembutal). Reflex discharges of motoneurons were routinely induced by shocks applied to dorsal roots or to the dorsal columns. Particular use was made of the fact that the first portion of the reflex discharges to these stimuli represents the direct activation of motoneurons by the primary afferent fibers after a single synaptic delay; the size of the first wave of the reflex discharge to a constant afferent volley is then a measure of the synaptic excitability of the motoneurons (Renshaw, 1940). Stimulating and recording leads were also applied to various groups of ventral rootlets, to mixed nerves of the leg, and to the branches to individual muscles of the hind limb. Spinal transections and the intradural cutting of dorsal roots were performed according to the requirements of specific experiments. The usual differential amplifier and stimulating apparatus were used.

RESULTS

1. Centrifugal discharge in motor fibers following an antidromic volley. A volley of impulses backfired toward the spinal cord over a group of motor fibers sets up, after a short central delay, a centripetally directed discharge in some motoneurons. A typical experiment is illustrated in Fig. 1. The seventh lumbar ventral root was severed intradurally and four electrodes were placed on each of two portions of it, *A* and *B*. A shock, approximately maximal for alpha fibers, delivered to *A* through electrodes *3* and *4* set up a volley of impulses which travelled centrally in the motor fibers. This was recorded at low amplification through electrodes *A1–2* (record *c*). Record *d*, at 25 times the amplification of *c*, clearly shows that the deflection due to the large centripetal volley was followed by a smaller diphasic response of reversed sign. Therefore the arrival of the antidromic volley at a central region evoked, after a short delay, a centrifugal discharge in some motor fibers. In records *a* and *b* the stimulating electrodes were placed central to the recording electrodes. The axons were killed under electrode *4*. Both the direct response to the shock and the delayed volley of central origin then appeared as monophasic deflections. The delayed volley of central origin is seen to have occupied 2 to 3 per cent of the number of fibers involved in the centripetal discharge which evoked it.

The centrifugal discharge following an antidromic volley also occurs in the large limb nerves, such as the tibial and peroneal nerves, and in the nerves to individual muscles of the leg. It appears after the dorsal roots which contain the sensory fibers of the nerve under examination have been cut.

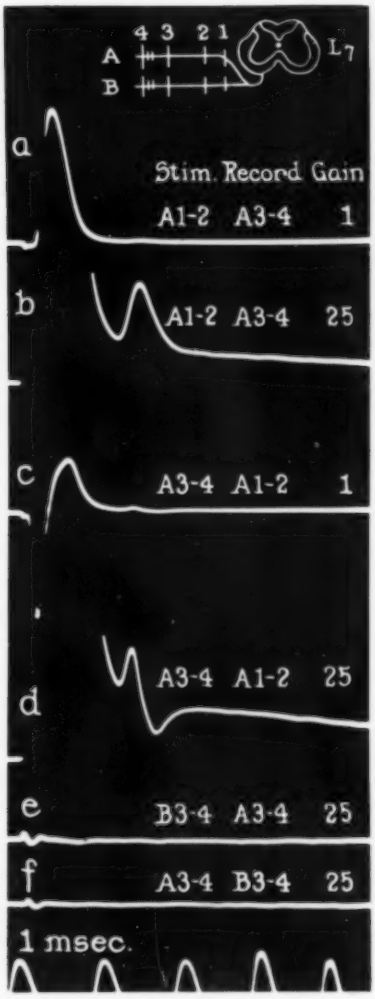


FIG. 1. Centrifugal discharges set up in motor axons by antidromic volleys. Cat under light anesthesia (Nembutal). The ventral rootlets of the 7th lumbar segment were divided into two equal groups, as shown in the inset. Relative amplification, stimulating and recording electrodes for each record are indicated on the figure. An antidromic volley in either group of rootlets produced a centrifugal discharge in some fibers of the same rootlets after a central latency of 0.9 msec. Stimulation of either group of rootlets produced no discharge in the other group (records *e* and *f*).

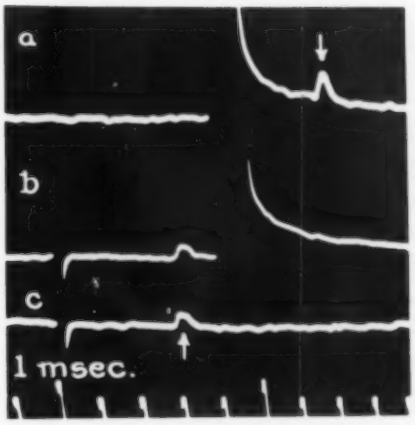


FIG. 2. The effect of an afferent volley on the centrifugal discharge which is initiated by an antidromic volley. Records from a small branch of the nerve to the semimembranosus of a cat under light anesthesia (Nembutal). The caudal cord had been transected, and all dorsal roots from the 4th lumbar to the caudal transection were severed on the testing side. The recording leads were placed distal to the stimulating electrodes on the prepared nerve in the thigh. *a*, antidromic volley. The deflection due to the centrifugal impulses, as marked by the arrow, appears later than the efferent discharges of Fig. 1, because of the greater conduction distance in the motor axons. *b*, the antidromic volley preceded by a shock applied to the dorsal columns at L_4. The efferent discharge following the antidromic volley was almost completely abolished. *c*, the small reflex discharge produced by the conditioning stimulus in isolation.

It is not possible to confuse the efferent discharge which follows an antidromic volley with spontaneous firing on the negative after-potential at the cut distal end of the prepared nerve. High partial pressure of carbon dioxide about the distal end greatly reduces the spontaneous firing without altering the centrifugal discharge.

Several additional facts point to a central origin for the discharge which follows an antidromic volley. Not only do the impulses of the discharge pass in a centrifugal direction (Fig. 1*d*), but their presence depends upon the integrity of the spinal cord. The efferent discharge is reversibly abolished during the subtotal asphyxia of the cord, which may be induced by temporary occlusion of the descending aorta at the level of the upper lumbar segments. Lastly, the centrifugal discharge is conditioned by a preceding dorsal root volley which fires few motoneurons (Fig. 2).

While these experiments demonstrate that the centrifugal impulses are set up at the spinal cord, they do not permit a more specific inference about its locus of origin. All that can be said is that the discharge arises at or central to the point of emergence of the motor axons from the cord.

The central latency for the centrifugal discharge evoked by an antidromic volley may be determined from the total latency by subtracting the conduction times in the motor axons for the centripetal and the centrifugal impulses. The total conduction time in the fastest motor axons may be approximated by the sum of the shock-response intervals for *m* waves (Lorente de Nó, 1939, page 409) set up by direct electrical stimulation of the motoneurons in the ventral horn and detected at the recording leads and at the stimulating cathode. These corrections for oscillogram *b* of Fig. 1 amount to *ca.* 0.3 msec. The minimal central latency, therefore, is *ca.* 0.9 msec., provided that some of both the centripetal and the centrifugal impulses pass in fibers of maximal or nearly maximal conduction velocity. This assumption is verified by the fact that apparent central latencies calculated in this way from records made on nerves in the thigh are equal to or only slightly greater than the central latencies calculated from the data of ventral root leads.

The central latencies for the centrifugal discharge generally lie between 0.8 and a little over 1.0 msec. The similarity of these values to the synaptic delays at motoneurons (Lorente de Nó, 1938; Renshaw, 1940) immediately suggests that the centrifugal impulses may arise from the synaptic excitation of motoneurons by impulses of the antidromic volley arriving over recurrent collaterals. Several lines of evidence render this possiblity very unlikely. Instead, the centrifugal discharge seems to be due to repetitive activity in a fraction of the antidromically activated motoneurons. It is, therefore, in some ways formally comparable with the "*effet pseudoréflexe*" of Arvanitaki (1938, page 101; 1940a).

First, the centrifugal discharge never appears in a group of motor fibers other than that in which the antidromic volley passes. This is true when the fibers used for stimulating and recording are groups of ventral rootlets from the same or from adjacent levels of the cord (Fig. 1*e* and *f*). It is also true when mixed nerves of the leg are used (dorsal roots cut), and the same result obtains with motor branches to the same or different muscles.

Second, contributory evidence comes from the relationship between the size of an antidromic volley and the size of the efferent discharge which it

produces. If the efferent discharge were synaptically excited, it would be expected that as the size of the antidromic volley approached its maximal value, the number of centrifugal impulses set up by it would decrease, owing to the large number of refractory motoneurons. Actually a roughly linear relationship exists between the numbers of centripetal and centrifugal impulses. Figure 3 shows some of the responses obtained in one experiment in which the stimulating shock was progressively increased from submaximal strengths to values supermaximal for A fibers.

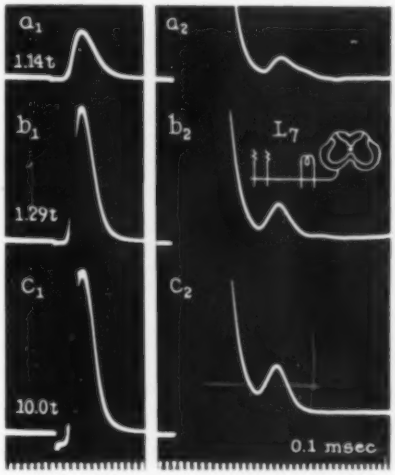


FIG. 3. The relation between the size of an antidromic volley and the size of the efferent discharge produced by it. Cat under light anesthesia (Nembutal). Stimulating and recording electrodes arranged as shown in the inset. On the left, low gain records to show the size of the volley directly initiated by the stimulating shock. On the right, records at 25 times the amplification to show the centrifugal discharges of central origin. Stimulus strength, expressed in terms of threshold value (1.0t), is indicated on the left for each pair of records.

Additional proof is supplied by the effects which an antidromic volley exerts upon the reflex discharges of other motoneurons. As stated above, an antidromic volley in isolation never sets up centrifugal impulses in other motoneurons. It does, however, condition the reflex discharges into other motor axons. A detailed discussion of these effects follows. In brief, the facilitation which may occur is always delayed; inhibitory effects on the other hand appear immediately upon the arrival of the antidromic impulses into the cord. Therefore, at the time an antidromic volley, which arrives at the cord in some motoneurons, is setting up its centrifugal discharge, it produces only inhibitory effects on the synaptic excitation of other motoneurons. The efferent discharge cannot, therefore, be in motoneurons other than those invaded by the backfired impulses. Detonator facilitation produced by the arrival of impulses at the terminal knobs of the recurrent collaterals has not yet been discovered. One might suppose that such excitation exists; but as far as other motoneurons are concerned, any such action is masked by a more effective inhibitory process acting at the same time.

2. Effect of antidromic volley in some motor fibers on reflex discharges of other motoneurons. Antidromic volleys in certain deafferented motor nerves condition subsequent reflex discharges into other motor branches (Fig. 4–8; Table 1). For a given pair of nerves the effect is relatively constant in different preparations. The conditioning is frequently inhibitory; but facilitation, usually preceded by inhibition, also occurs.

An antidromic volley in one group of ventral rootlets often acts to inhibit subsequent testing discharges in the motor axons of adjacent rootlets. In contrast to the results ob-

tained when motor nerves are used for conditioning and testing, the effects are variable and sometimes absent. The reason for the relative constancy of the conditioning effect when motor nerves, rather than groups of ventral rootlets, are used is obvious in the light of cer-

Table 1. Effects of antidromic volleys in some motor nerves on reflex discharges into other motor nerves

	Motoneurons occupied by conditioning volley	Tested motoneurons	Effect of conditioning volley on tested reflex*
Conditioning volley and tested reflex in motor nerves to the same muscle or muscle group	biceps (one part)	biceps (another part)	Inhibition (33, 65)
	biceps (one part)	semitendinosus	Inhibition (50, 64, 75, 70, 75, 20)
	semitendinosus	biceps (one part)	Inhibition (80, 40, 85, 20)
	biceps (one part)	semimembranosus	Inhibition (60)
	semimembranosus	biceps (one part)	Inhibition (92)
	semimembranosus (one part)	semimembranosus (another part)	Inhibition (35)
	semimembranosus	semitendinosus	Inhibition (35)
	medial head of gastrocnemius	lateral head of gastrocnemius	Inhibition (50, 33, 50, 75)
	lateral head of gastrocnemius	medial head of gastrocnemius	Inhibition (60, 60)
	quadriceps (one half)	quadriceps (other half)	Inhibition (10, 10, 15, 10, 10)
	sartorius (one part)	sartorius (remainder)	Inhibition (60, 70)
Conditioning volley and tested reflex in nerves whose motoneuron pools lie in different portions of the ventral horn	tibial	peroneal	Facilitation (to 140 percent), preceded by slight inhibition
	peroneal	tibial	No significant effect observed
	tibial	hamstring	Inhibition (61, 85)
	hamstring	tibial	Inhibition (80, 85), followed by facilitation (118, 120)
	peroneal	hamstring	Inhibition (75, 82)
	hamstring	peroneal	Inhibition (85, 92)
	hamstring	quadriceps	Inhibition (54, 88, 95)
	quadriceps	hamstring	Facilitation (117)
	tibial	quadriceps	Inhibition (76)
	quadriceps	tibial	Slight facilitation (?)
	peroneal	quadriceps	Slight inhibition (?)
	quadriceps	peroneal	No significant effect observed
	quadriceps	sartorius	No significant effect observed
	sartorius	quadriceps	Slight inhibition
	sartorius	gracilis	No significant effect observed
Conditioning volley and tested reflex in motor nerves to individual antagonistic muscles	gastrocnemius	tibialis anticus	Slight facilitation
	tibialis anticus	gastrocnemius	No significant effect observed
	extensor longus digitorum	flexor longus hallucis	No significant effect observed
	flexor longus hallucis	extensor longus digitorum	No significant effect observed

* The figures in parentheses represent the maximal conditioning seen in specific experiments and expressed as:

$$\frac{\text{size of conditioned reflex}}{\text{size of unconditioned reflex}} \times 100.$$

tain anatomical details (Sherrington, 1892; Marinesco, 1904; Cajal, 1909; Bok, 1928). The fibers of any small ventral rootlet are the axis cylinders of motoneurons lying in the cord at approximately the segmental level at which the rootlet makes its exit. They lie scattered throughout the cross-section of the ventral horn at this segmental level (Cajal). The motoneurons associated with any given muscle, on the other hand, extend continuously over two or more segments of the cord; but their cell bodies always occupy a specific, restricted locus in the cross-section of the ventral horn (Marinesco, Bok). The motor axons to each muscle thus arise from cells occupying a specific portion of the ventral horn. They become randomly mixed with other motor fibers in the ventral roots, and eventually segregate again into the motor nerve. The segmental variation in the innervation of any particular muscle is considerable, but the neurons representing the various muscles always preserve the same relative positions longitudinally in the cord (Sherrington). Thus in all preparations the motoneurons supplying any muscle stand in the same axial and cross-sectional relationship to those of every other muscle. No such fixed relationship exists between the motoneurons supplying any two groups of rootlets.

Control experiments demonstrate that antidromic conditioning as shown in Fig. 4 to 8 depends upon the arrival at the cord of impulses in motor A fibers. (i) The routine procedure has been to section the dorsal roots at, above, and below the segments which typically receive afferent fibers from the antidromically stimulated nerve. More extensive deafferentation in a few experiments has served to exclude the possibility that the conditioning is mediated by impulses in aberrant sensory fibers. In one such experiment the cord was transected at both caudal and upper lumbar levels. All dorsal roots on both sides of the isolated lumbosacral segments were cut intradurally. Impulses from the periphery could then arrive only via the intact motor roots. A shock applied to the dorsal columns at L4 served to set up a small discharge in a motor branch to the quadriceps. This discharge was inhibited by a preceding antidromic volley in the other branches of the crural nerve, just as when only the homolateral lumbar and sacral dorsal roots had been severed. (ii) The records of Fig. 4 demonstrate that impulses in the A fibers of the conditioning nerve are the ones which produce the inhibition. In the experiment from which the records of Fig. 4 are taken, stimulation of the homolateral dorsal columns at L4 produced a discharge in the nerve to the lateral head of the gastrocnemius (record *a*). In the following records (*b*–*e*) the column stimulus was preceded by a shock applied to the nerve of the medial head of the gastrocnemius. The inhibi-

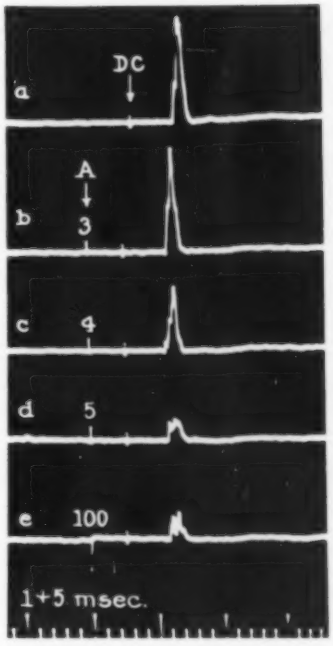


FIG. 4. The conditioning of motor discharges into the nerve to the lateral head of the gastrocnemius by antidromic volleys in the nerve to the medial head of the gastrocnemius. Decerebrated cat. The caudal cord had been transected and all dorsal roots as far cephalad as the second lumbar were severed on the tested side. *a*, motor response evoked by stimulation of the dorsal columns at L4. *b*–*e*, the same preceded by a shock to the nerve of the medial head. Relative stimulus strengths indicated on the figure.

tion of the reflex increased as the conditioning shock was strengthened from threshold to a value maximal for A fibers (record *d*). A 20-fold increase of the stimulus (record *e*) then produced no additional effect. (iii) The remote possibility that the antidromic volley produces conditioning peripherally rather than centrally has been excluded. The greatest conditioning effect is produced when the antidromic volley has entered the cord several milliseconds before the reflex impulses leave, a time at which the large peripheral changes due to the action currents of the antidromic impulses would have

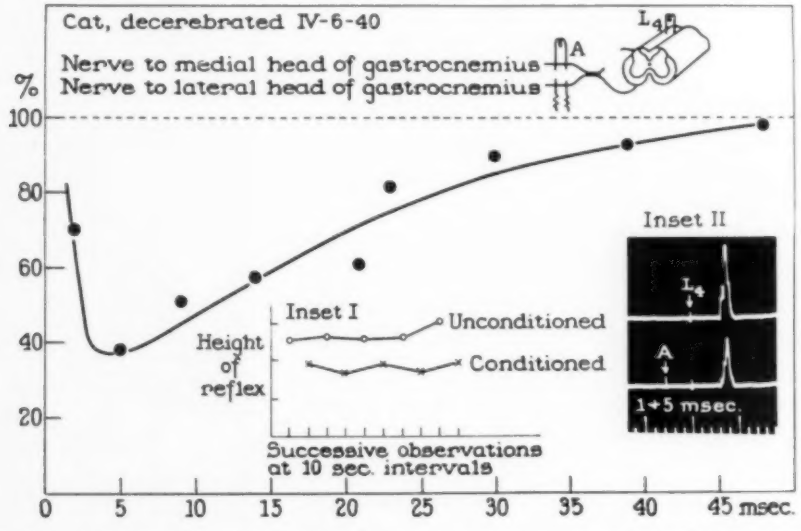


FIG. 5. Inhibition of motor discharges in some motoneurons by antidromic volleys in other motoneurons. Ordinates: $\frac{\text{average height of conditioned reflex}}{\text{" " " unconditioned "}} \times 100$. Abscissae: interval at which the testing shock followed the conditioning stimulus. Same experiment as Fig. 4. The cell bodies of the conditioning and the tested motoneurons occupied the same portion of the ventral horn. Inset I, the individual observations on which the point to the extreme left is based. Inset II, typical unconditioned and conditioned reflex responses from this experiment.

disappeared. Furthermore, when motor discharges are known to have been set up in motor fibers, as after electrical stimulation, they are never affected by antidromic volleys in other motor fibers.

The most conspicuous effect of an antidromic volley in some motoneurons on the discharges of others is found when the conditioning and tested nerves are branches to the same muscle or muscle group. The two pools of motoneurons then occupy the same portion of the ventral horn, axially as well as cross-sectionally. In all such experiments the effect of the antidromic volley has been inhibitory. The inhibition has a characteristic time course which is shown in Fig. 5. In the experiment reproduced in this figure the caudal cord was transected, and all the dorsal roots on the right side were severed from L2 to the caudal transection. A stimulus applied to the right

dorsal column at L4 produced a motoneuron discharge which was recorded in the nerve to the lateral head of the homolateral gastrocnemius. This discharge was inhibited by a preceding antidromic volley backfired into the motoneurons supplying the medial head of the gastrocnemius. As shown in Fig. 5, the inhibition reached a maximum when the testing impulses were set up shortly after the antidromic volley. The response deficit then gradually declined and disappeared as the shock interval approached 50 msec. Similar results were obtained from experiments with the various branches to the hamstring muscles, with branches to the quadriceps, and with branches to the sartorius (Table 1).

Of particular interest is the fact that the inhibition of a tested discharge by an antidromic volley in a related group of motoneurons appears when the antidromic volley reaches the cord as late as simultaneously with the testing impulses which fire the motoneurons after a single synaptic delay. The illustrative data of Fig. 6 are taken from an experiment in which the conditioning volley and the tested motor discharge occupied the two principal branches to the quadriceps. The caudal cord was transected and all homolateral dorsal roots as far cephalad as L1 were severed intradurally. The conditioning curve is shown in Fig. 6A. It is clear from Fig. 6B, which shows the data on which the point x of 6A is based, that the testing response was definitely inhibited when the conditioning shock preceded the testing stimulus by only 0.7 msec. Oscillograms taken with the stimuli in this temporal relation appear in Fig. 6C. The sequence of potential changes evoked by the conditioning antidromic volley and recorded with a needle electrode within the ventral horn is shown in the upper record. The middle record shows the unconditioned testing response, and the lower record the testing response inhibited by an antidromic volley set up 0.7 msec. before the testing impulses.

More significant than the shock interval is the relationship between the time of arrival of the antidromic volley at the cord and the period of the central latency for the tested motor discharge. Most of the motoneurons of the quadriceps group are located in L5 and L6 (Sherrington, 1892). The upper record of Fig. 6C shows that impulses of the antidromic volley reached the ventral horn of these segments 0.8–0.9 msec. after delivery of the conditioning shock. Direct electrical stimulation of the motoneurons at L5–L6 produced an *m* wave (Lorente de Nó, 1939, p. 409) at the recording electrodes after 0.8 msec. Therefore, 0.8 msec. was approximately the time taken for the tested motor impulses to travel from the cord to the recording electrodes. Thus the second arrows in the lower two records of Fig. 6C indicate the time at which these impulses left the cord. Records from the dorsum of the cord show that the testing impulses arrived at L5–L6, 0.2–0.3 msec. after the testing shock, as indicated by the first arrows on the lower records of Fig. 6C. The central latency of the testing reflex in these segments is given by the interval between the arrows—*ca.* 0.9 msec., or the duration of a single synpatic delay (Lorente de Nó, 1938; Renshaw, 1940). It is apparent from these conduction times that when the conditioning shock preceded the test-

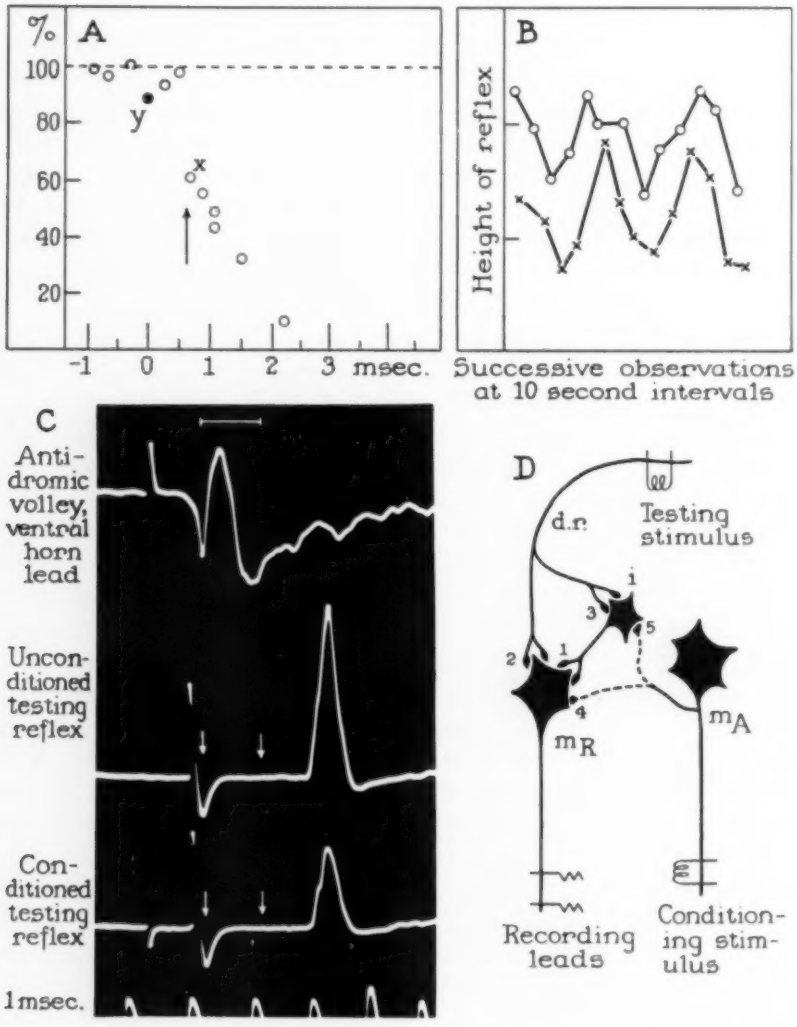


FIG. 6. Conditioning of motor discharges into part of the crural nerve by antidromic volleys in other branches to the quadriceps. Cat under light anesthesia (Nembutal). The caudal cord had been transected, and all sacral and lumbar dorsal roots on the tested side were cut. The tested "reflexes" were initiated by stimulation of the dorsal columns at L4. 6A, the conditioning curve, ordinates and abscissae as in Fig. 5. The arrow indicates the time at which the conditioning and testing volleys reached the ventral horn simultaneously. 6B, the data on which point *x* of 6A is based. Note the definite inhibition superposed upon a slow rhythmic variation of the discharge. 6C, oscillograms identified on the figure. The abscissae are on the same scale as those of 6A. The conditioning and testing shocks have the temporal relations of point *x* of 6A. 6D, a diagram to show all the possible neurons and synaptic connections which might have been concerned in the production of the response deficit at point *x* of 6A.

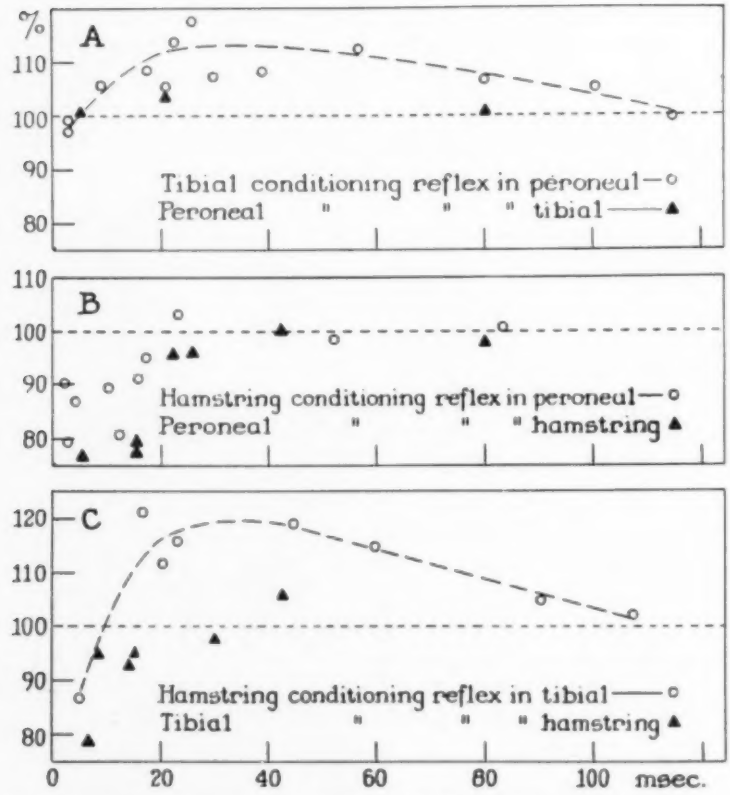
ing stimulus by 0.6–0.7 msec., the fastest antidromic impulses and the testing impulses in the primary neurons reached the region of the quadriceps motoneuron pool at the same time. This time is indicated by the arrow in Fig.

6A. Inhibition (point x) was already pronounced when the testing impulses arrived very slightly after the conditioning volley. Thus inhibition was first induced when an antidromic volley arrived approximately simultaneously with the testing impulses which fired the tested motoneurons after a single synaptic delay. When the antidromic impulses arrived a little earlier, they produced a greater inhibition; but when they arrived later, no facilitation was apparent.

Conditioning of the discharges of some motoneurons by antidromic volleys in other motoneurons also occurs when the conditioning and tested motor nerves are not branches to the same muscle or muscle group (Table 1). Although it is apparently necessary that the two pools of motoneurons occupy the same segmental levels of the spinal cord, their cell bodies need not lie in the same portion of the ventral horn. The effects for most pairs of nerves are relatively small. Also, as never occurs when the two motoneuron groups occupy the same place in the ventral horn, facilitation is sometimes observed.

In Fig. 7 are shown the conditioning curves obtained in one illustrative experiment in which the antidromic volleys and tested motor discharges occupied the motoneurons of the tibial, peroneal and hamstring nerves. The segmental distribution of the motoneurons of each of these three nerves was determined at the end of the experiment by measuring the size of the motor volleys set up in each nerve by stimulation of the various lumbar and sacral ventral roots. The results are tabulated in Fig. 7D. The comparative similarity in the axial distribution of the motoneurons supplying the three nerves stands in contrast with the cross-sectional segregation of the three groups of cell bodies (Fig. 7E, after Marinesco). In confirmation of Forbes *et al.* (1933), an antidromic volley in the peroneal nerve did not significantly condition reflex discharges into the tibial nerve (Fig. 7A). However, an antidromic volley in the tibial did affect subsequent reflex discharges into the axons of the peroneal nerve. It produced a prolonged period of facilitation of the two-neuron arc discharge to an afferent volley (Fig. 7A, also 8). The facilitation appeared only when the tested impulses followed the conditioning volley by several milliseconds. Initially slight inhibition, which was more apparent in other experiments, occurred. An antidromic volley in the hamstring nerve inhibited the motor discharge into the peroneal, and vice versa (Fig. 7B). An antidromic volley in the tibial likewise inhibited motor discharges into the hamstring nerve, but in the reverse relation the initial inhibition gave way to prolonged facilitation (Fig. 7C).

The conditioning effect of an antidromic volley in one group of motoneurons is not dependent upon the origin of the impulses that serve to excite the tested motoneurons. A shock applied to the ventral columns excites fibers which produce, after a single synaptic delay, a discharge of motoneurons located 2 to 3 cm. caudad of the stimulating electrodes (Lloyd, 1941a). The collaterals which the ventral column fibers send to the ventral horn are oriented, on the average, in the direction opposite to the reflexo-



D Segmental distribution of motoneurons (by experiment)

Segment	Peroneal	Tibial	Hamstring
L_4	0.0%	0.0%	0.0%
L_5	0.2	0.3	0.0
L_6	4.2	3.3	17.9
L_7 upper ½	52.3	31.1	25.0
L_7 lower ½	42.3	42.1	41.1
S_1 upper ½	1.0	11.6	14.2
S_1 lower ½	0.0	10.9	1.7
S_2	0.0	0.5	0.1

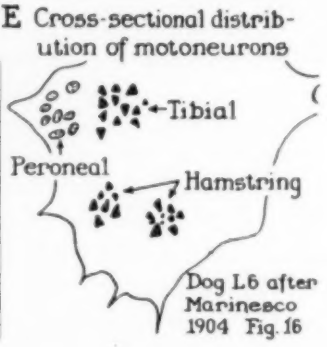


FIG. 7. The interaction between motoneuron discharges and antidromic volleys in the tibial, peroneal, and hamstring nerves of a cat under light anesthesia (Nembutal). The sacral cord had been transected, and all dorsal roots as far cephalad as L3 were severed on the tested side. The motoneuron discharges ("reflexes") were evoked by stimulation of the dorsal columns at L4 with one or two shocks. A, antidromic volley in the tibial nerve conditioning the motor discharge into the peroneal (○); vice versa (▲). B, antidromic volley in the hamstring nerve conditioning the discharge in the peroneal (○); vice versa (▲). C, antidromic volley in the hamstring nerve conditioning the discharge into the tibial (○); vice versa (▲). D, the segmental distribution of the motoneurons of the tibial, peroneal, and hamstring nerves of this preparation. E, the positions of the motoneuron pools of the tibial, peroneal, and hamstring nerves in the cross-section of the ventral horn (after Marinesco). The cell bodies of the peroneal motoneurons show retrograde degeneration.

motor collaterals of the primary afferent neurons. Yet the conditioning effects of an antidromic volley in one group of motoneurons upon the discharges of another group are the same whether the tested motoneurons are excited by ventral column volleys or by impulses in primary afferent neurons. The records of Fig. 8 demonstrate this fact for both inhibitory and facilitatory effects.

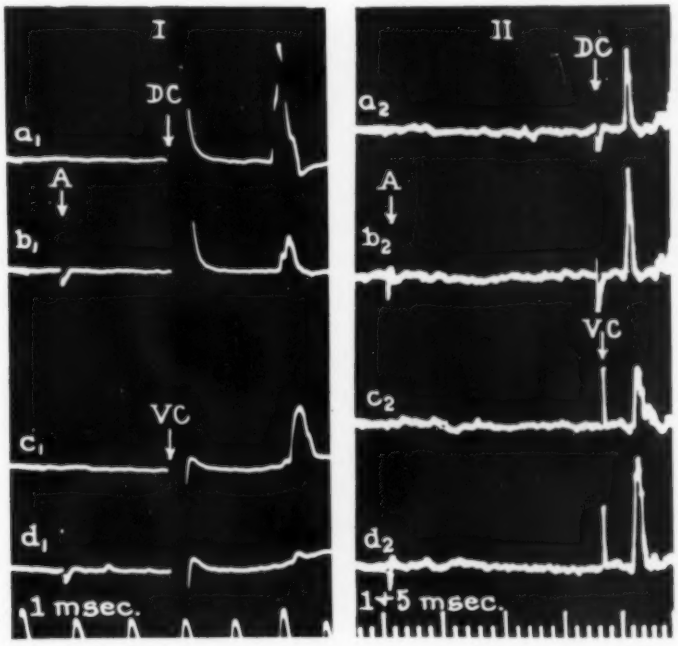


FIG. 8. The conditioning by antidromic volleys of reflexes initiated by testing impulses in primary afferent fibers (*a*, *b*) and in ventral column fibers (*c*, *d*). Column I, same experiment as Fig. 6. Conditioning volleys and tested motor discharges in two nerves to the quadriceps. The tested discharges are inhibited. Column II, conditioning antidromic volleys in the tibial nerve; tested discharges in the peroneal. The tested discharges are facilitated. From an experiment on a cat under light anesthesia (Nembutal). The cord was transected at L1 and in the caudal region; all dorsal roots on the tested side of the isolated lumbar and sacral segments were severed. The conditioning produced by the antidromic volleys is similar, whether the tested discharges are set up by ventral column activity or impulses in primary afferent neurons.

The magnitude of the conditioning effect, although not its qualitative nature, is dependent upon the size of the tested motor discharge. As Tables 2 and 3 show, the larger the tested discharge, the less is the fractional inhibition or facilitation produced by a fixed conditioning volley. This is because the actual number of motoneurons removed from or added to the motor discharge by the conditioning volley increases relatively little. The affected motoneurons may be assumed to be those stimulated approximately at threshold by the testing volley.

Table 2. Motor discharge in nerve to tibialis anticus, set up by stimulation of dorsal column at L5 and conditioned by a preceding antidromic volley in nerve to gastrocnemius. Dorsal roots cut. IV-13-40

Relative size of tested 2-neuron arc discharge into nerve to tibialis anticus	$\frac{\text{Size of conditioned discharge}}{\text{Size of unconditioned discharge}} \times 100$	Per cent facilitation	Relative number of facilitated motoneurons
1	126	26	1.0
6	105	5	1.15

Table 3. Motor discharge in nerve to semitendinosus, set up by stimulation of the dorsal column at L5 and conditioned by an antidromic volley in a branch to the biceps; stimulus interval, 5.5 msec. Dorsal roots cut. IV-16-40

Relative size of the tested 2-neuron arc discharge into nerve to semitendinosus	$\frac{\text{Size of conditioned discharge}}{\text{Size of unconditioned discharge}} \times 100$	Per cent inhibition	Relative number of inhibited motoneurons
1	64	36	1.0
2	80	20	1.1
4	88	12	1.3
20	96	4	2.2

Discussion

It is most unlikely that antidromic conditioning volleys in the present experiments significantly altered the testing volleys in fibers of either the primary afferent neurons or the ventral columns before the impulses reached the ventral horn. For a large safety factor is associated with the propagation of impulses in axons (Hodgkin, 1937; Tasaki, 1939); and, except in the ventral horn, activity of the conditioning motoneurons produces very little current flow which might polarize axons and block conduction. Similarly, there is no evidence that impulses once initiated in the tested motor axons are blocked by antidromic volleys in other axons (page 174). An antidromic volley produces its conditioning effect either by altering the excitability of neurons to synaptic stimulation or by altering the stimuli delivered to postsynaptic elements by the testing impulses in axonal terminations.

It has been shown that activity in one group of motoneurons can condition the activity of another group (Fig. 4 to 8). The initial effect is a response deficit, which is present when the conditioning volley reaches the ventral horn at the beginning of the synaptic delay at the tested motoneurons (point *x* of Fig. 6A). Available for the explanation of these facts are: (i) the arrival of conditioning impulses at the terminal knobs of recurrent collaterals, and (ii) other effects not primarily dependent upon synaptic associations. The present data do not permit a complete resolution of the mechanisms for the conditioning. Some delimitation, however, is possible for the mechanism of the initial inhibitory effect. Inhibition such as that at

point *x* of Fig. 6A cannot be explained by the sequelae of detonator excitation associated with the arrival of conditioning impulses at the terminals of recurrent collaterals, as shown in hypothetical form at *4* and *5* of Fig. 6D, because detonator effects at these terminals would be expected to sum with those of testing impulses arriving simultaneously at endings *2* and *3* to produce facilitation. It is, therefore, necessary to conclude that the well-known detonator (excitatory) process associated with the arrival of impulses at synapses is not the only mechanism by which an active neuron can affect other nerve cells. This conclusion is corroborated by recent observations on inhibition in which the conditioning volleys occupy primary afferent fibers (Lloyd, 1941b).

The role played by the recurrent collaterals of spinal motoneurons is not known. Hence any explanation for the antidromic conditioning (inhibition, or as the case may be, facilitation) which involves the collaterals is purely speculative. Of the other possible mechanisms there comes to mind most prominently the polarizing action of electrical currents. Currents are in fact set up in the ventral horn by the activity of the conditioning motoneurons (Fig. 6C), and it is known that flow of current through the cord alters the size of testing two-neuron arc discharges (Renshaw, 1940). The only question is whether the currents set up in the cord by the conditioning motoneurons are large enough to produce the effects observed.

For conditioning to occur, the conditioning and the tested motoneurons must lie at the same segmental levels of the cord. A variety of curves is found when the two groups of motoneurons occupy the same axial position but different parts of the cross-section of the ventral horn (cf. Fig. 7). It is obvious that the observed inhibition and facilitation, whatever their basis, must depend upon details of the anatomical substratum in the ventral horn which are as yet unknown. The conditioning effects are not obviously related to reciprocal innervation (cf. Table 1).

The reduction of the tested discharges of motoneurons by their active neighbors in the same pool (Fig. 5) has approximately the same time course as the subnormality of the activated motoneurons to synaptic stimulation (Eccles, 1931; Gasser, 1939; Lorente de Nó, 1939). Thus the firing of some motoneurons in any nucleus produces a decrease in the responsiveness of most or all the motoneurons in the pool. Thereby the susceptibilities of the motoneurons to firing by premotor neurons would be synchronized.

The effects produced by a centripetal volley in a mixed nerve upon reflex discharges into the motor axons of other nerves have commonly been assumed to be referable entirely to impulses in primary afferent axons. The present findings emphasize that effects produced by the antidromic impulses in the motor axons cannot be disregarded.

Summary

An antidromic volley in a group of motoneurons produces a small centrifugal discharge from the spinal cord into some of the motor axons which

carry the antidromic impulses. No centrifugal impulses appear in the axons of other motoneurons. The centrifugal impulses appear to be repetitive discharges set up at some central portion of the motoneurons, rather than reflex discharges synaptically excited through recurrent collaterals.

Antidromic volleys do, however, condition synaptically excited discharges of other motor cells. Inhibition typically occurs if the tested and the conditioning motor nerves are branches to the same muscle or muscle group. The response deficit then reaches its maximum when the conditioning antidromic volley arrives at the cord 2 to 4 msec. before the tested motor discharges are set up. The amount of inhibition then gradually declines. It disappears when the antidromic volley precedes the tested discharge by *ca.* 50 msec.

A particularly significant feature of the inhibition is its early onset. A response deficit is present if the antidromic volley reaches the ventral horn simultaneously with the testing impulses which fire the tested motoneurons after a single synaptic delay. This finding cannot be explained on the assumption that the only effect which an active neuron exerts upon other neurons is the detonator excitation produced by the arrival of impulses at synapses.

Conditioning also occurs when the antidromic volleys and the tested motor impulses occupy the nerves to different muscles or muscle groups. Both facilitation and inhibition have been observed. Facilitation usually follows a brief initial period of inhibition. Maximal facilitation is attained when the conditioning antidromic volley precedes the tested discharge by *ca.* 25–30 msec. It then declines and disappears only when the interval between conditioning and tested volleys exceeds 100 msec.

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A DIRECT CENTRAL INHIBITORY ACTION OF DROMICALLY CONDUCTED IMPULSES

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FIBERS, or synaptic endings of fibers, having an inhibitory action, have often been invoked to provide a mechanism by which to explain central inhibition. There has been no direct evidence to support the contention that such fibers or endings exist in the mammalian central nervous system (Gasser, 1937). Furthermore, subnormality (Graham, 1935) of central neurons serves as a mechanism to explain central inhibition without employing other than known processes, provided central neurons are activated prior to the appearance of inhibition (Gasser, 1937). Activation of central neurons is almost inevitable if the central latency of inhibition is greater than the minimal synaptic delay of approximately 0.5 to 0.6 msec. (Lorente de Nó, 1935, 1938). Therefore, to postulate an active inhibitory process requires a demonstration of inhibition under circumstances which preclude the possibility of subnormality in accounting for a response deficit. In effect, the paths taken by the inhibitory action and the necessary testing excitatory action must not have elements in common before impinging upon the final common path (the motoneurons); and motoneurons must not have been discharged by the conditioning impulses, for as Renshaw (1941) has shown by antidromic conditioning, active motoneurons exert an inhibitory action on adjacent motoneurons, which begins without measurable latency and parallels the subnormality of the active motoneurons. The general argument that forces the establishment of these rigid criteria has been clearly stated by Lorente de Nó (1936).

In the experiments presented here the testing excitation was derived from dorsal root collaterals to motoneurons (Cajal, 1890, 1894) which mediate the two-neuron arc discharge (Renshaw, 1940), or from the tract fibers of the ventrolateral columns, which discharge the motoneurons with a single synaptic delay when stimulated within approximately 3 cm. of the motoneuron pool (Lloyd, 1941). The inhibitory effect to be discussed is exerted between the time of arrival of primary afferent impulses (in fibers other than those available to the testing shock), and the time at which the first *de novo* impulses are initiated in central neurons. Hence the rigid conditions imposed above are satisfied in the present experiments.

Cats were used in all experiments. They were lightly narcotized with Dial (approximately 0.5 ml./kilo), after which the lumbosacral spinal cord was exposed and the appropriate roots were carefully prepared for stimulation and recording.

Inhibitory action. Figure 1 illustrates the direct inhibitory action of primary afferent impulses on motoneurons. The impulses exerting the inhibitory action were initiated by a single shock delivered to the sixth lumbar

(L6) dorsal root. The inhibited motoneurons were those that contribute axons to the first sacral (S1) ventral root. A test of the excitability of these motoneurons was obtained by means of single shocks delivered to the S1 dorsal root. The early impulses discharged into the S1 ventral root in response to the S1 dorsal root shock are mediated without the intervention of interneurons. In Fig. 1A and I show the response of the motoneurons to the testing S1 dorsal root shock in isolation; the two-neuron arc discharge is identified by an arrow. In Fig. 1B the conditioning L6 shock and the testing S1 shock were delivered simultaneously with a notable decrease in the two-

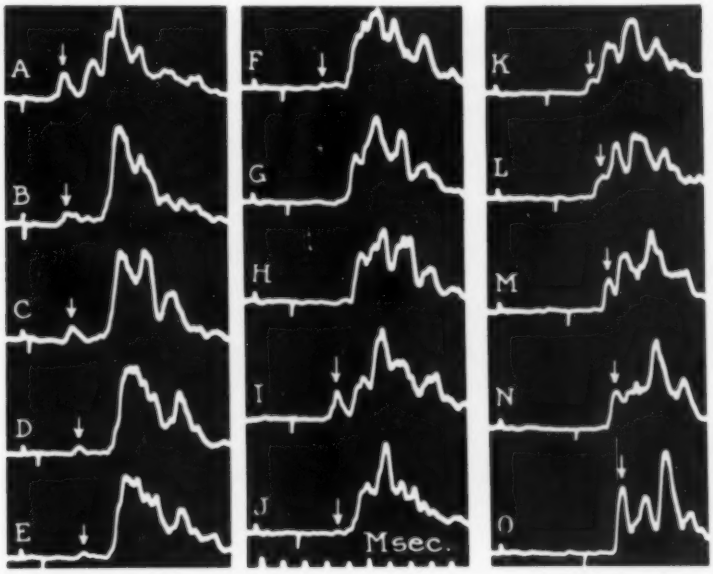

FIG. 1. Inhibition of earliest reflex discharge. Conditioning shock delivered to L6 dorsal root. S1 motoneurons tested by ipsilateral S1 dorsal root shock. The early reflex discharge elevation, recorded from the S1 ventral root, is identified by an arrow except in G and H, where this elevation cannot be clearly distinguished. A and I are motoneuron responses to the test shock in isolation. Further details in text.

neuron arc discharge. When the S1 shock succeeds the L6 shock by increasing intervals, inhibition of the two-neuron arc discharge progresses to completion during the second millisecond (Fig. 1, C to H), after which recovery occurs and inhibition passes over into facilitation (Fig. 1, J to O). In other experiments, inhibition was maximal at stimulus intervals of 1 msec. or less.

Figure 2A shows in graphical form an experiment similar to that illustrated in Fig. 1, but in another preparation. The amplitude of the two-neuron arc discharge is plotted as ordinates against the interval between the two shocks, as abscissae. The combination of roots used was the same as in Fig. 1. At the zero time abscissa the two shocks are simultaneous. At points to the left of zero the testing S1 shock antecedes the conditioning L6 shock. At points to the right of zero this relationship of shocks is reversed.

Inhibition of the two-neuron arc discharge begins when the impulses in the two dorsal roots are approximately synchronized, and it progresses for slightly less than 1 msec., after which the discharge increases in a regular manner to the normal range and into facilitation. It may be stated with reasonable surety that the upswing in the motoneuron discharge, starting just before 1 msec. has elapsed, coincides with the arrival at the motor nucleus of the excitatory impulses of the first internuncial relay. It is clear, therefore, that the inhibition described here begins without measurable latency and achieves considerable intensity before any relayed impulses are initiated in the spinal cord. The total duration of the inhibitory action is not measurable, since it may be curtailed or obscured by the arrival of the relayed excitatory actions. The dorsal root shock threshold for the inhibitory effect has been found to coincide with that of the alpha fibers of the dorsal root.

The records shown in Fig. 2 (B to M) are similar to those used for constructing the curve 2A, and are taken from the same preparation. They were, however, recorded on a slower time axis. Figure 2B shows the motoneuron response to the conditioning L6 dorsal root shock, beginning after some 3 msec. latency. Figure 2C is the motoneuron response to the S1 dorsal root testing shock. The earliest reflex volley, which is used as an indicator, is marked by an arrow. In Fig. 2D, the L6 and S1 shocks are applied simultaneously, while in Fig. 2 (E to M) the testing S1 shock follows the L6 shock by increasing intervals. The inhibition and subsequent facilitation of the two-neuron arc discharge appears as in graph 2A.

Locus of inhibition. It might be supposed, since dorsal root fibers have been used for the initiation of both the conditioning and the testing impulses, that "blocking" of impulses could occur in the dorsal columns (Barron and Matthews, 1935, 1936), presumably at the collateral junctions. On the same supposition, "blocking" could occur at the junction of collaterals to the dorsal horn nuclei, or to the intermediate nuclei. Finally, without prejudice as to its nature, the inhibitory effect could be located within the nexus of the motoneurons themselves. The parallel orientation of pathways from neighboring dorsal roots, which permits a multiplicity of possible loci for interaction, may be avoided by substituting a ventrolateral column test volley for the dorsal root test volley.

The collaterals of ventrolateral column fibers have a general orientation in the opposite sense with respect to the central grey substance of the ventral horn. Furthermore, impulses in the two sets of collaterals reach common ground only within the confines of the motor nucleus at the time intervals at present under survey. Therefore, if inhibition of the motoneuron response to a ventrolateral column volley parallels the inhibition of motoneuron response to a dorsal root volley, the only acceptable locus for the inhibitory action under discussion is within the motor nucleus. Figure 3 shows that this parallelism holds.

Figure 3A is the response of the S1 motoneurons to a single S1 dorsal

root shock. In 3B to 3F the S1 dorsal root shock is preceded, at increasing intervals, by a single shock to the L6 dorsal root, the response to which in isolation is seen in 3G. Figure 3H is the response of the same S1 motoneuron pool to a single ventrolateral column shock applied within 3 cm. of the motoneuron pool. In 3I to 3M, the ventrolateral column shock is preceded by the

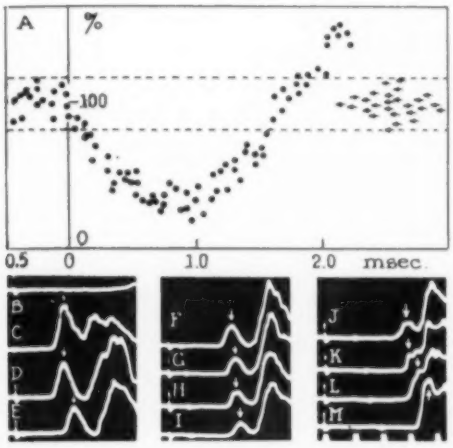

FIG. 2. Inhibition in another preparation. A, graph showing decrease in amplitude of two-neuron arc discharge, expressed as percentage of control values, and plotted against the time interval between conditioning and testing shocks. The arrows show the amplitude values for 26 control observations, the spread of these values being expressed by the broken lines. B to M are observations similar to those from which graph A was constructed. B, motoneuron response to the conditioning L6 shock. C, response to testing S1 shock. In D to M the S1 shock follows the L6 shock at increasing intervals. The two-neuron arc spike potential is marked by an arrow throughout. Time in 1 msec. intervals below record M.

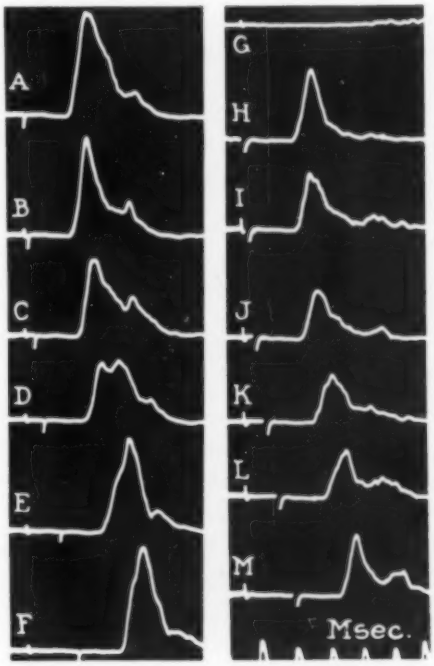

FIG. 3. The left-hand column shows inhibition of motoneuron response to a dorsal root shock, while the right-hand column shows inhibition of motoneuron response to a ventrolateral column shock. The responses to the two test shocks in isolation are seen in A and H respectively. G is the response to the conditioning shock in isolation.

L6 dorsal root shock at increasing intervals. All of the observations of Fig. 3 were made on a background of internuncial activity occasioned by an earlier column shock of subliminal strength for motoneuron response. Such an intensified background is not a necessary condition for the performance of the experiment, but it does show that facilitated test responses are subject to the inhibitory action, as are test responses obtained from the "resting" spinal cord.

Since all other circumstances are identical, the observations 3H to 3M with the use of column test volleys may be compared directly with the observations 3A to 3F, with the use of dorsal root test volleys. By this direct

comparison it is seen that the inhibitory action of the L6 impulses is similarly revealed by the dorsal root test shock and by the ventrolateral column test shock. Therefore, the dorsal root impulses must exert their inhibitory action at the motoneuron, or in the immediate neighborhood of the motoneuron.

Table 1. Spatial distribution of conditioning effects in regions at and caudal to entry zone of selected dorsal roots

Source of conditioning activity	Motoneurons tested	Effect of conditioning activity during first msec.
Ipsilateral L5	S1	0 Fig. 5A
Contralateral L6	Lower L7	0 Fig. 4B
Contralateral L7	L7	0
Contralateral L6	S1	0
Ipsilateral L5	L7	Progressive inhibition
Ipsilateral L6	S1	Progressive inhibition as in Fig. 1, 2, and 3
Ipsilateral L6	Lower L7	Facilitation passing into inhibition. Fig. 4A.
Ipsilateral L7	S1	Facilitation passing into inhibition
Upper half Ipsilateral L7	S1	Decreasing facilitation as in Fig. 5B.
Lower half Ipsilateral L7	S1	Strong facilitation as in Fig. 5C.
Upper half Ipsilateral S1	S1	Strong facilitation

Table 1 shows the effect of impulses in dorsal roots which are orientated anatomically in several ways with respect to the tested motor nuclei. Several of the results tabulated are presented in detail in Fig. 4, which compares (A) the conditioning effect of an ipsilateral shock with that (B) of a symmetrical contralateral shock, and in Fig. 5 which shows the conditioning effect of impulses in various ipsilateral rootlets arranged anatomically at several distances cranial to the tested motoneurons. It is clear from Table 1 and Fig. 4 and 5 that inhibitory actions, as well as excitatory actions, of primary afferent fibers are exerted in levels which are supplied directly by the parent descending collaterals of those primary afferent fibers. This has

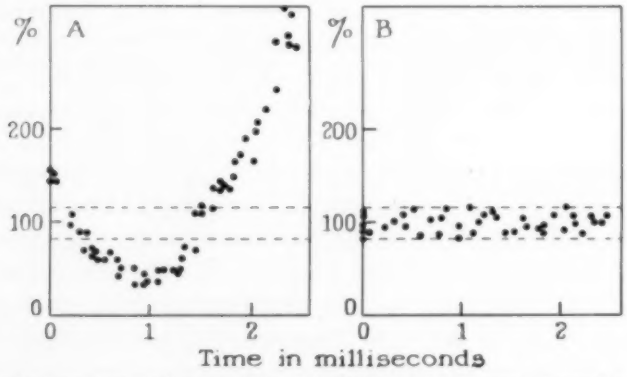

FIG. 4. Graphs constructed as in Fig. 2A. The motoneurons tested are those sending axons to the lower half of the L7 ventral root. In A the response of these motoneurons is conditioned by an ipsilateral L6 dorsal root shock, In B, a contralateral L6 shock is substituted for the ipsilateral L6 conditioning shock.

been confirmed by direct observation of the conducted intramedullary spike potential. It is impossible, because of the lack of exact anatomical knowledge, to state with complete confidence that the motoneurons at all the levels at which effects are demonstrable are in synaptic relation with collaterals from the primary afferent fibers stimulated by the conditioning shock. However, with the reservations enforced by imperfect anatomical knowledge it appears probable that the fibers which cause an effect, whether the effect be excitatory or inhibitory, enter the nucleus in which that effect is exerted.

Figures 1, 2 and 4 show that, although the inhibitory effect is well established before the time at which the first postsynaptic elements can be activated, it lasts beyond the time at which interneurons are certainly active. In fact, inhibition, established before interneurons are active, may become more profound after the time when interneurons must be active. Therefore, it is probable that some interneurons may exert an inhibitory action in their own right, just as do the collaterals of primary afferent fibers.

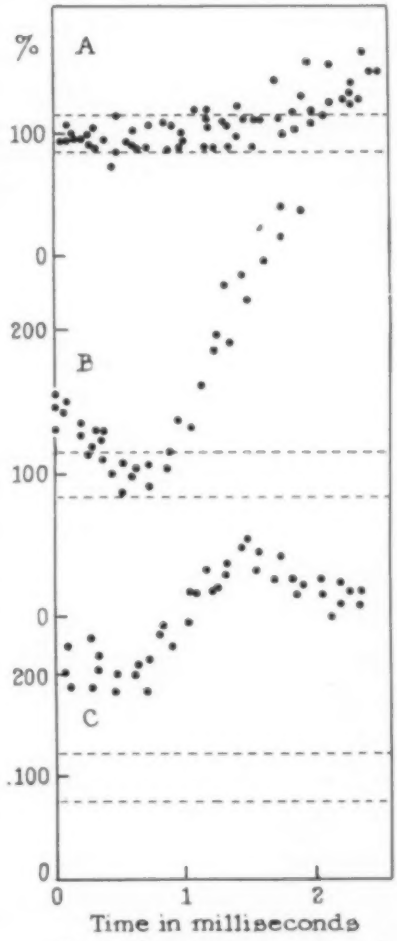

FIG. 5. Graphs constructed as in Fig. 2A. S1 motoneuron response is conditioned by ipsilateral dorsal root shocks. These shocks were delivered to L5 dorsal root in A, to the upper half of L7 dorsal root in B, and to the lower half of L7 dorsal root in C.

Comment. In assessing the specificity of the inhibitory action, it is of interest to compare the excitability changes in Fig. 5C, in which S1 motoneurons are conditioned by stimulation of the lower half of the ipsilateral L7 dorsal root, and the excitability changes in Fig. 2A, in which S1 motoneurons are conditioned by stimulation of the ipsilateral L6 dorsal root. The curves 5C and 2A are from the same experiment with the use of the same testing volley, the result of a single maximal alpha shock to the ipsilateral S1 dorsal root. Let us now consider a point on the two curves before there is a possibility of initiation of postsynaptic impulses, and late enough to avoid any confusion introduced by difference in conduction time of the several volleys. A point about 0.3 to 0.4 msec. on the time scales would fulfill these conditions. At this point of time, the S1 motoneuron pool, under the influence of the sequelae of the L7 shock, discharges approximately twice the number of impulses in the test response volley as it does when not so influ-

enced. On the other hand, when influenced by the sequelae of the L6 shock, the S1 motoneuron pool discharges but half of the impulses in the test response volley as it does when not so influenced. This difference is a fact that must be accommodated by any hypothesis made to explain direct central inhibitory action. As a first approximation the difference could be accounted for (i) by an important difference in the spatial relationship of impulses with respect to the motoneurons at the time in question, or (ii) by endings of specific effect. It is certain that the inhibition is a direct action without measurable latency. It would seem from this fact that the effect must be electrical. However, with the finer anatomy of the system and synaptic transmission as little understood as they are today, it would serve no useful purpose to pursue speculation further.

Summary

A direct inhibitory action of primary afferent fibers, exerted upon the activation of motoneurons by primary afferent collaterals or ventrolateral column collaterals, has been demonstrated.

The inhibition occurs without measurable latency.

The inhibitory effect is exerted within the confines of the motor nucleus.

It is probable, although not proven, that some internuncial impulses exert a comparable inhibitory action.

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EFFECTS OF LESIONS TO CORPUS STRIATUM UPON SPONTANEOUS ACTIVITY IN THE MALE RAT

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RICHTER and Hawkes (2) reported marked increase in the spontaneous activity of rats subjected to lesions in the frontal portions of the brain. We (1) found that injury to the anterior or posterior cerebral cortex of the male rat sometimes resulted in heightened activity; but in other cases activity decreased after operation. In this study animals sustaining lesions to the frontal cortex suffered varying amounts of invasion to the corpus striatum. However no consistent relationship was discovered between striatal lesions and postoperative changes in activity.

Richter and Hines (3) reported permanent increases in activity resulting from gross removal of the frontal poles of the brain in five macaques. Unilateral removal of the frontal cortex followed by removal of the tip of the striatum regularly produced more marked and precipitous increases in activity than could be elicited by cortical destruction alone. In one animal similar results were obtained with bilateral lesions to the neo-cortex and striatum. These workers concluded that activity is controlled through the prefrontal cortex and the striatum.

Having been unable completely to confirm Richter and Hawkes' results that frontal lesions inevitably produced postoperative increases in the running activity of rats, we have investigated the effects of striatal lesions upon the activity of this animal. It seemed possible that differences between our findings and those of the earlier investigators might be due to variations in lesions inflicted below the neocortical level.

PROCEDURE

Five male rats 9 months old were placed in the standard activity cages employed in our previous work and in that of Richter and Hawkes. This cage includes a small living chamber adjacent to a 10-inch circular drum. Revolutions of the drum in either direction are recorded on a cyclometer.

After a 30-day preoperative period (which previous results prove ample for high reliability), during which daily readings of activity were taken, each male was subjected to brain operation and returned immediately to the activity cage. Lesions were placed in the corpus striatum by passing direct current into the selected region via a fine wire electrode. Destruction, by electrolysis, is confined to tissue immediately surrounding the uninsulated tip of the electrode.

The rats remained in activity cages 50 days after the operation, at which time they were sacrificed, brains were removed, sectioned at 50μ, and stained with thionin.

Results and conclusions. In Table 1 is presented the pre- and postoperative performance of each animal. Rat 1 showed a definite increase in activity following the operation. Numbers 3 and 4 were less active after the operation, and Nos. 2 and 5 exhibited no change in activity.

RAT 1
RAT 2
RAT 3
RAT 4
RAT 5
LEVEL 1
LEVEL 2
LEVEL 3
LEVEL 4
LEVEL 5
LEVEL 6
LEVEL 7
LEVEL 8
LEVEL 9
LEVEL 10
LEVEL 11
LEVEL 12
LEVEL 13
LEVEL 14
LEVEL 15
LEVEL 16
LEVEL 17
LEVEL 18
LEVEL 19
LEVEL 20
NC
CC
CS
ALC
LV
PHC
CAC
OC
GLM
CN

Figure 1 illustrates the lesions inflicted in each case. There is no clear relationship between the amount of destruction or the locus of the lesion and its effect upon activity. Rat No. 1 sustained the largest lesion and showed postoperative increase in activity. Number 3 with the second largest opera-

Table 1. Average revolutions per day before and after partial destruction of the corpus striatum

	Days	Rat				
		1	2	3	4	5
Normal	0–4	4	349	324	111	131
	5–9	1	133	285	59	141
	10–14	2	116	241	70	57
	15–19	69	110	145	55	38
	20–24	23	172	106	43	65
	25–29	37	177	82	36	80
Daily average as normal		23	173	198	61	85
Operated	0–4	52	17	64	21	38
	5–9	446	76	96	40	48
	10–14	262	207	58	5	87
	15–19	226	338	63	10	70
	20–24	43	155	37	2	83
	25–29	113	193	74	6	130
	30–34	168	246	117	22	126
	35–39	240	201	103	25	91
	40–44	173	110	91	20	117
	45–49	180	103	83	31	108
Daily average as operate		180	181	78	19	90

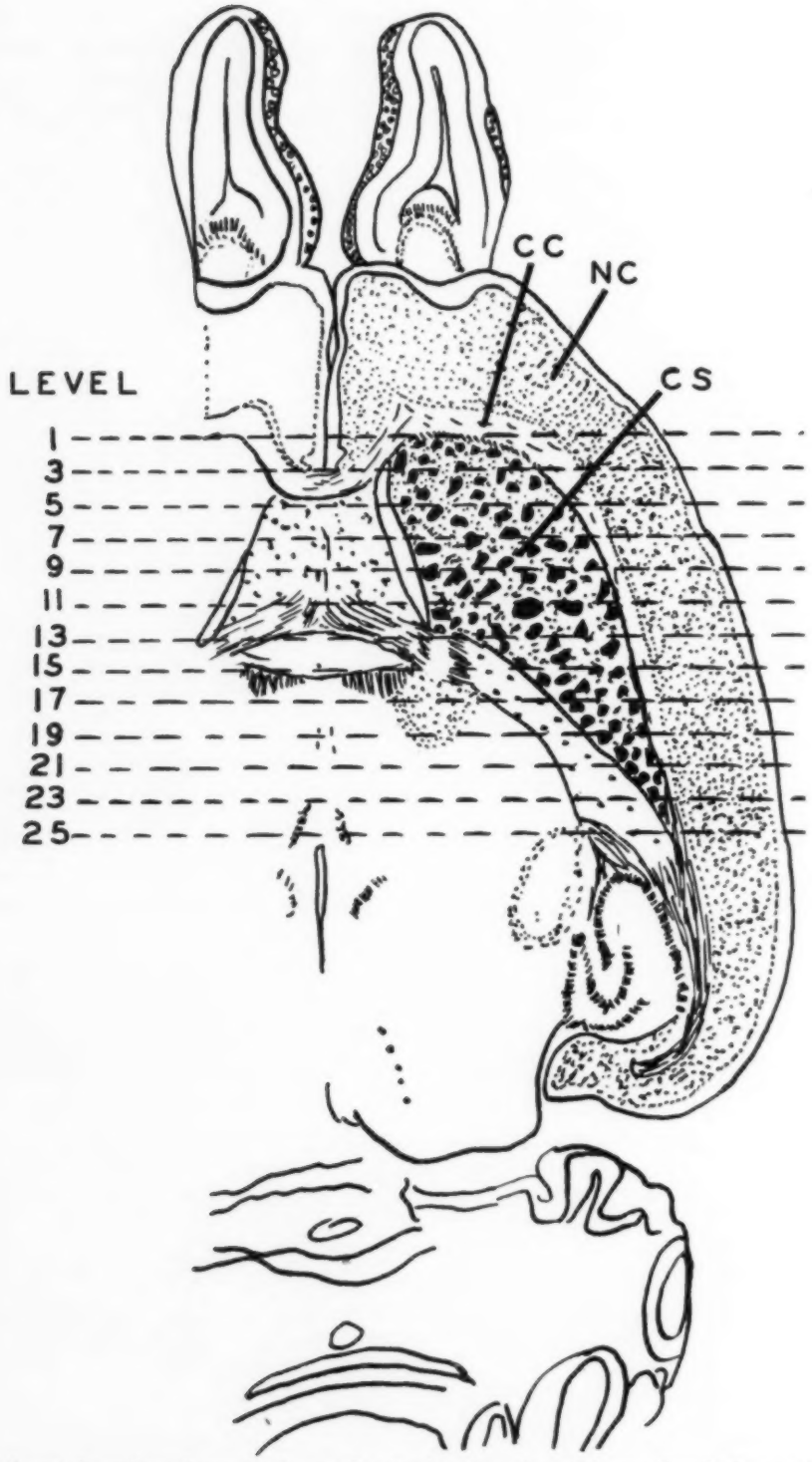
tion was less active as a result of the brain injury. (None of these animals exhibited any marked indications of motor difficulty following the operation. Within three days locomotion appeared to be normal.)

The only conclusion justified by these data is that destruction of the corpus striatum (within the limits herein investigated) has no consistent effect upon running activity in the male rat. There is no clear-cut indication that in this animal the striatum exerts a controlling influence over activity.

FIG. 1. Each brain is represented by epidioscope tracings of five cross sections. The first and last sections represent the beginning and end of the lesion; and intermediate sections have been selected at evenly spaced intervals. The "level number" in the upper right corner of each traced section refers to the levels shown in the dorsal view of the corpus striatum sketched on the opposite page.

Landmarks in the cross sections are labelled as follows:

ALC anterior limb of anterior commissure
CAC crossing of anterior commissure
CC corpus callosum
CN head of caudate nucleus
CS corpus striatum (lesion in black)
FHC first fibers of hippocampal commissure
GLH granular layer of the hippocampus
HC hippocampal commissure
LV lateral ventricle
NC neocortex
S septum
OC optic chiasma



Horizontal section through the rat brain showing the arbitrary levels from which various cross sections traced in Figure 1 were taken.

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FUNCTIONAL ANATOMY OF BRACHIUM PONTIS†

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INTRODUCTION

THE BRACHIUM pontis forms the final neuronal pathway of the cortico-ponto-cerebellar tracts. The anatomic relationships of this system have given rise to numerous and divergent theories concerning its functional significance, but convincing experimental data have been notably lacking. The present study was undertaken in an effort to determine the effects of discrete, anatomically controlled lesions of the brachia pontis. Because of the conflicting results previously reported by both experimental and clinical observers, as well as the possible implications of the anatomic connections of the middle cerebellar peduncle, a broad program of observations was carried out. Psychobiological tests were designed to demonstrate execution and retention of learned behavior patterns, volitional motor skills, and hand-eye coördination. Observations of cerebellar functions, posture, gait, equilibrium, muscle tone, and personality characteristics were included. The periods of study of three animals here reported covered from 5 to 20 months and were concluded by histologic verification of the lesions.

MATERIALS AND METHODS

For studies of learned behavior the animals were trained preoperatively and tested postoperatively on six different types of problem boxes. The first five boxes: rope box, crank box, pull box, hook box, and hook and handle box, were identical with the problem boxes used and described by Jacobsen (1931). The sixth box, sliding door box, had on the side facing the animal a sliding door. By raising the door the animal exposed the interior of the box containing an ordinary tin cup inverted over the food. Peanuts and pieces of orange and banana were used as motivation. Careful quantitative records were kept of the animals' performance.

The coördination, general motor activity, gait and equilibrium were recorded in detailed behavior notes taken daily. Equilibrium was further tested by utilizing a catwalk, a piece of 2″ x 4″ beam some six feet long. Hand-eye coördination was measured in two ways. A gross method involved suspending a bit of food from a piece of string and swinging it in various planes and at varying speeds within reach of the animal. The other method consisted of placing bits of food on the turntable of a modified Victrola. The accuracy and regularity with which the animals captured the food was then noted for three speeds, slow, medium and fast. Tonus of the extremities, patellar and brachial reflexes, and hopping and placing reactions were measured after the animals had reached an optimum state of relaxation. The different personality traits of the various animals were noted daily in the protocols, and changes in general attitude were carefully watched for after each of the operations.

Operative procedure: Under intraperitoneal nembutal anaesthesia, a large occipito-parietal bone flap was elevated and the dura opened widely. The venous connections to the lateral sinus and the posterior portion of the superior sagittal sinus were fulgurated and

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divided. The occipital lobe was gently elevated, exposing the falx, which was opened by a semilunar incision extending through the edge of the incisura. The anterior aspect of the cerebellum was slowly elevated as fluid was evacuated from the pontine cistern. The petrosal vein was coagulated and divided, exposing the angle formed by the trigeminal nerve with the facial and acoustic nerves at the pons. The middle cerebellar peduncle was identified at this point and a small nerve hook inserted below the inferior margin of the peduncle. The peduncle was completely divided by gentle traction on the hook, without damage to the superior cerebellar artery. The occipitoparietal dural flap was replaced but not sutured, to allow escape of cerebrospinal fluid from the subdural space. The bone flap was replaced and the scalp wound closed.

Protocols

The three experimental animals herein reported were as follows:

Case 1. *Mangabey; Male, Wt. c. 5 kg.* The right middle cerebellar peduncle was sectioned March 3, 1937. An attempt to section the left middle cerebellar peduncle on July 7, 1937, resulted in death of the animal.

Microscopic examination revealed that section of the right middle cerebellar peduncle had been virtually complete, with the possible exception of a few of the innermost fibers in the posterior region which might, however, be part of the most anterior portion of the restiform body. No damage to any of the underlying structures in the brainstem could be observed.

Case 2. *Java macaque; Female, Wt. c. 2.5 kg.* This animal had had the right lateral lobe of the cerebellum previously removed by Dr. Fulton. The left middle cerebellar peduncle was sectioned November 18, 1936. From examination of serial sections it appeared that the left middle cerebellar peduncle had not been completely severed, since some of the more medial strands of fibers were seen to be intact. Moreover, on the right side some portions of cerebellar cortex remained, especially near the vermis and in the various sulci.

Case 3. *Mangabey; Male, Wt. c. 5 kg.* The left middle cerebellar peduncle was sectioned May 25, 1936. The right middle cerebellar peduncle was sectioned September 21, 1936. Abridged protocol notes for this animal will be given as representative of the symptomatology which follows section of the brachium pontis.

First operation on May 25, 1936, the left middle cerebellar peduncle was sectioned.

May 26. Animal is groggy but moderately active. It holds its head markedly to the left. Nystagmus is present, with the quick phase to the right and a slight rotary component. It is unable to use its right leg, and uses both hands in taking food to its mouth. Swallowing appears to be difficult, and the line of the mouth droops to the left.

May 27. Animal is quite active but suffers from obvious vertigo. Falling is to either side indiscriminately. It shows marked dysmetria in use of the right hand, but no tremor is evident. No nystagmus is present. Corneal reflex is absent on the left, and the muscles of mastication are weak on that side. It is rapidly regaining the use of its right leg. Wound is clean, and the flap shows no elevation.

May 29. Animal is tested on problem boxes, all of which it solves in less than 4 sec. It uses either hand swiftly and without errors, save for slight dysmetria. Its legs are used incoördinately in locomotion, the animal mostly pulling itself forward with its forelegs. It holds its head noticeably to the left, and tends to fall to either side. The legs are used fairly well in climbing, in which procedure it shows an obvious spiralling to the left.

June 1. The animal is beginning to use its legs more effectively in locomotion, although the hind quarters still sag when it is on all fours. Its head is held now nearer the midline. Some spiralling and circus movements are still present.

June 8. Animal now uses its legs quite well in walking. There is no tendency to circus movement or spiralling. It can even walk on the hindlegs alone, lifting its feet well with each step, and with good balance.

June 22. The posture of the animal and its use of all four extremities in walking, climbing, etc., are no different now from its preoperative state. The left corneal reflex is still absent. No dysmetria is observable. The general behavior of the animal is similar to its preoperative state: frisky, inquisitive, coöperative.

Second operation on September 21, 1936, the right middle cerebellar peduncle was sectioned.

Sept. 21. 9 p.m. Animal is sitting up in cage. Its spine curves to the right and head is bent far onto the right shoulder. There is some ptosis of the right eyelid. Occasional spontaneous movement of the right arm occurs. Grasp is good with the right hand. When supported in the air, it kicks vigorously with both hind feet.

Sept. 22. Animal holds its head far to the right. There is marked nystagmus, with the quick phase to the left and slightly downward. No tremor is observable in any of the extremities, although there is a slight unsteadiness of the head which simulates a tremor. Wound is clean and shows no elevation.

Sept. 23. Animal's right cornea is cloudy and the right eyelid puffy. Nystagmus is now almost imperceptible. A slight tremor (?) of the head on the neck is still noticeable. There is rather marked dysmetria, but it is hard to evaluate in view of the obvious ocular difficulties.

Sept. 26. Animal is active and inquisitive. It falls heavily when it tries to move about rapidly. Right cornea is now cleared. No nystagmus can now be observed. Some hypometria is present with either right or left hand. Head is held to the right most of the time, but it straightens it to midline when engaged in a voluntary act—*e.g.* picking up a piece of food.

Oct. 29. The animal walks with a slapping down of the feet to the floor. The feet are not lifted well, and hind quarters sag greatly. Marked circus movement to the right is apparent, and it spirals to the right in climbing. In manipulating objects it tends to work with the left hand while supporting itself with the right arm extended. The spine curves to the right whenever it attempts voluntary movement with either upper extremity. Both legs show some hypotonia on passive manipulation.

Nov. 12. The animal shows absolutely no deficits when tested on the problem boxes, save on the turntable problem in which it is difficult to keep it interested. On the boxes it seems to favor using the right hand more than preoperatively.

Nov. 16. The animal shows the same sort of squat "duck walk" as previously, walking on the full soles of its feet. It now raises its hind quarters about one-half the normal height from the floor. The coördination of hindlimbs with forelimbs is poor. Some spiralling is still present, though circus movements are not particularly apparent. Hopping and placing reactions are normal.

Dec. 9. When the animal holds to the lead chain in walking its legs show a shuffling, incoördinate gait. When the chain is removed and it is allowed to stroll about by itself, it raises its hind quarters well—though still not quite to their normal height—and proceeds more or less like a normal animal. Passive manipulation does not seem to indicate any measureable hypotonia in the lower extremities, yet there is a faltering in the gait and a trembling of the thigh muscles of the right leg when the animal puts weight on it.

Mar. 16, 1937. The animal's walking now differs only subtly from the normal. The hind quarters are not held quite to the normal height, and it tends to place its feet very carefully and to walk on the full sole of the foot. It makes no spontaneous attempts to run, jump, or climb. The coördination of the extremities is now almost, but not quite, normal. There is a subtle lag which is hard to define, and yet its gait is obviously not the easy, rhythmic gait of the normal animal. One gets the impression that the animal must constantly "watch its step," and this may be borne out by the fact that when forced to run, the incoördination between the hindlimbs and the forelimbs becomes more marked, with the result that it loses its balance and falls.

Apr. 29, 1937. Gait remains unchanged since Mar. 16. The animal now seems rather sluggish and lethargic. The problem of finding suitable motivation for the animal in the learned behavior tests grows more and more difficult. The coördination between the hindlimbs and the forelimbs is still delicately out of rhythm, and it uses a somewhat broader base than the normal animal.

Sept. 30, 1937. The gait of the animal seems to show a more exaggerated lack of coördination than at the beginning of the summer. Base seems broader, and it appears to exert more effort in an attempt to keep its extremities correlated in locomotion. It cannot maintain itself on the catwalk, not even when it attempts merely to sit still. There is no constancy to the direction of falling. Tonus seems equal in all extremities. No dysmetria, tremor, or other classical cerebellar signs are observable.

Dec. 10, 1937. The animal's condition is similar to that reported on Sept. 30, save that all symptoms have increased greatly in severity. It is now very sluggish and expressionless, quite unresistant to handling, deliberate and lethargic in all its behavior. Its facial expression is fixed.

Findings. The animal was sacrificed on Dec. 15, 1937 and the central nervous system removed for study. On microscopic examination the right brachium pontis appeared to have been completely sectioned without any damage to underlying structures. The lesion of the middle cerebellar peduncle on the left included all the fibers of this system save some dubious strands which mingle with the anterior portion of the restiform body. There was no evidence of damage to brainstem structures on the left side. No other pathologies were noted at autopsy.

Table 1. Symptoms following section of brachium pontis.

Symptom	Case 1. Mangabey Rt. side only	Case 2. Java (Rt. cerebellum removed) Lt. br. pontis	Case 3 Mangabey Lt.	Case 3 Mangabey Rt.
		Transient Symptoms		
Spiralling around long axis of body	++ to rt.	+ to lt.	++ to lt.	++ to rt.
Curvature of head and trunk	++ to rt.	+ to lt.	++ to lt.	++ to rt.
Incoördination of gait	++	++	++	+++
Nystagmus (slow phase)	++ to rt.	+ to lt.	++ to lt.	++ to rt.
Dysmetria	+	+	+	+
Tremor	0	0	0	0
Ataxia	0	0	0	0
Hypotonia	++ left + right	++ left	+ left + right	+ left + right
Solving problem boxes	Normal	Normal	Normal	Normal
Hopping and placing reactions	Normal	Normal	Normal	Normal
Deep reflexes	Normal	Normal	Normal	Normal
General behavior	Sluggish	Sluggish	Sluggish	Sluggish
		Permanent Symptoms		
Hand-eye coördination	Normal	.....	Normal	−20 to −30%
		Progressive Symptoms		
Equilibratory disorders	0	++	0	+++
Incoördination of gait	0	++	0	+++
General behavior	0	Sluggish	0	Sluggish

Results

The symptoms occurring after section of the brachium pontis (Table 1) display such constancy of appearance and progression as to indicate the presence of a definite syndrome. The symptoms may readily be divided into three groups: transient, permanent, and progressive.

Transient symptoms

Of the symptoms in this group the following are the most significant: *Spiralling around the long axis of the body* appears in conjunction with *curvature of the head and trunk* to the side of the lesion. Such a forced posture

results in circus movements to the operated side, seen prominently during locomotion and other progression movements of the animals. These were the cardinal symptoms of lesions of the brachium pontis as reported by early observers (See Sherrington 1900; Schiff 1858). Until the work of Ferrier and Turner in 1894 there was considerable dispute concerning the direction of these movements. Symptoms of this kind usually disappear by the end of two to three weeks.

Incoördination of gait is quite striking after section of the middle cerebellar peduncle. This incoördination resolves mainly into an inability to correlate the hindlimbs with the forelimbs in locomotion. For a week to ten days after unilateral operations the animals are hardly able to use the hindlimbs at all, locomotion consisting of a crawling with the forelimbs and a dragging and shuffling of the hind quarters. By the end of three to four weeks, however, a unilaterally operated animal can usually not be differentiated from a normal one with respect to gait. In bilaterally operated monkeys the gait never quite returns to normal, but instead suffers a progressive disturbance, as will be discussed shortly.

Nystagmus is usually present for a few days after each operation, the slow phase being toward the operated side. *Dysmetria* may likewise be present transiently. That these two symptoms might be due to local irritation in the neighborhood of the operative site is suggested by the fact that their disappearance often coincides with the recovery of local signs referable to the V and VII cranial nerves.

No tremors in either voluntary or associated movements were noted at any time. Similarly *no ataxia* of the classical cerebellar type was observed. The incoördination of gait previously mentioned did not resemble a true cerebellar ataxia, especially since the upper extremities were spared. Again, the deficit seemed to be mainly a lack of coördination between the hindlimbs and the forelimbs rather than the characteristic cerebellar ataxic syndrome.

The *hypotonia* following section of the middle cerebellar peduncle was the most variable of the postoperative symptoms, although in each case it was significantly greater in the lower extremities than in the upper ones. In Case 1 it seemed most pronounced on the side opposite the lesion, though present bilaterally. In Case 2 the homolateral side was affected almost exclusively. In Case 3 both sides seemed equally affected. The hypotonia tended to disappear concomitantly with the forced postures.

The behavior of the animals in *solving the problem boxes* was in no observable way affected by section of one or both brachia pontis.

Deep reflexes and the *hopping and placing reactions* demonstrated no significant changes after section of the middle cerebellar peduncles.

Following unilateral section of the middle cerebellar peduncle the *general behavior and attitude* of the monkeys were transiently depressed and sluggish. These signs usually disappeared in unilaterally operated animals within

three to four weeks. After bilateral operation the sluggishness tended to progress, and the facial expression became fixed.

Permanent symptoms

A significant permanent symptom was observed in the fact that the bilaterally operated Mangabey (Case 3) showed a *diminution of hand-eye coördination* amounting to some 20–30 per cent below its preoperative norm. No lasting deficit of hand-eye coördination was noted in the unilaterally operated animals.

Progressive symptoms

Of the symptoms in this category three were most striking: an increasing difficulty in coördination of gait, a certain progressive dysequilibrium, and a gradual slowing down and lethargy in general behavior.

After virtual or actual bilateral interruption of the fibers of the brachia pontis (Case 2, Case 3) the locomotion of these monkeys never quite returned to normal. There remained for some 7 to 10 months a subtle faltering and a slight incoördination, of the same general type seen immediately after unilateral section of the peduncle, although greatly less in severity. By the end of approximately 10 months, however, the gait of these bilaterally operated animals was seen to become more and more affected. The gait became progressively more incoördinate (though again not resembling a true cerebellar ataxia) until after the lapse of 12 to 14 months the animals had extreme difficulty in progression even over a flat floor. Sudden sagging of the hind quarters would occur, and the animals tended to fall spontaneously, with no constancy to the direction of falling. Such animals were totally unable to walk along the catwalk, and some *equilibratory disturbance* seemed manifest in the fact that they could not even sit quietly on the catwalk without swaying and falling. Their falling and other equilibratory behavior while walking on smooth flat surfaces appeared more like a vestibular phenomenon than like any form of pulsion.

In those animals in which the brachium pontis fibers were bilaterally interrupted there occurred a *progressive sluggishness*. The facial expression and emotional behavior bore a suggestive resemblance to the human extrapyramidal Parkinsonian syndrome, although at no time were any rigidities, tremors or other abnormal movements noticeable.

Discussion

A tabular outline of experimental cerebellar "syndromes" based upon recent investigations is shown in Table 2. One of the most striking features illustrated in relevant current literature is the remarkable degree of compensation which follows even extensive lesions. However, since neocerebellar function is a relatively advanced phylogenetic acquisition it is not surprising that this should occur. It is probably significant that compensation becomes

less complete as the primate scale is ascended. The relative bilaterality of cerebellar function is likewise notable.

The positive characteristics of cerebellar lesions are tremor, hypotonia, equilibratory disorders, ataxia and disturbances of gait. Tremor has been especially associated with lesions of the dentate nucleus or its efferents in the

Table 2

Lesion	Animal	Syndrome	Investigator
Neocerebellar ablation	Macaca mulatta	Very transient tremor & ataxia	Keller, Roy & Chase, 1937
	Macaca mulatta baboon	Awkwardness, hypotonia & disturbance of gait, 4–6 weeks	Botterell & Fulton, 1938c
	Chimpanzee	"Hypotoria, slowness & slight awkwardness of volitional movement"	Botterell & Fulton, 1936
Cerebellar vermis	Macaca mulatta baboon mangabey	"Serious and enduring disturbances of equilibration."	Botterell & Fulton, 1938b
Nodulus & uvula	Macaca mulatta green monkey mangabey baboon chimpanzee	Lower folia plus nodulus and uvula: disequilibration; nodulus and uvula: disequilibration, rotation of head, rotation in running, jumping, climbing	Dow, 1938b
Inferior cerebellar peduncle	Macaca mulatta	Dysmetria, hypotonia, ipsilateral weakness, diminished reflexes, 2–3 weeks	Ferraro & Barrera, 1935
Superior cerebellar peduncle	Macaca mulatta baboon	Ataxia, tremor, dysmetria & decomposition of movement in ipsilateral extremities	Walker & Botterell, 1937
All three peduncles, unilateral	Macaca mulatta baboon	Ipsilateral ataxia, tremor, disturbances of equilibrium & gait up to 8 weeks	Botterell & Fulton, 1938a

superior cerebellar peduncle. Hypotonia appears after diverse cerebellar injuries, but, in the monkey, is apparently not a significant feature of the chronic picture. Equilibratory disorders are probably related to the vestibular system, especially after lesions to the medial cerebellar nuclei and the flocculonodular lobe. Forced positions and movements are likely in the same category. It is notable that *disturbances of gait* appear with sufficient frequency and duration to constitute a common denominator for neocerebellar lesions. The comparative anatomic development of the neocerebellum with

the assumption of the upright posture is perhaps significant in this connection.

Although the present report is chiefly concerned with behavioral studies, it is perhaps allowable to sketch certain functional anatomical possibilities. The ponto-cerebellar tracts carry numerous fibers whose impulses arise from widespread areas of the cerebral cortex and which finally come to play upon the Purkinje cells of the cerebellar hemispheres. That interruption of these tracts should produce extensive functional loss or diminution of these Purkinje cells seems logical.* It is not unlikely that the functional loss thus produced is more widespread than that following cerebellar cortical lesions previously reported. Cerebellar efferent impulses presumably pass from the Purkinje cells through the dentate nucleus and traverse the dentato-rubro-thalamic tract in the superior cerebellar peduncle. Their final effect may be mediated through the rubrospinal tract or directly upon the cerebral cortex through the thalamo-cortical fibers.

Concerning the question of cerebello-cortical impulses, the observations of Walker (1938) are of interest. Walker has shown that faradic stimulation of the lateral lobes of the cerebellum is reflected in changes of the resting action potentials of the cerebral motor cortex. From his observations Walker formulates the theory that the normal function of the neocerebellum may quite possibly be that of adding to the motor area a certain "dynamic tone." Other oscillographic studies by Dow (1938a) indicate that postural tone in the extensor muscles (*e.g.* plantaris) of the cat is inversely proportional to the functional activity of the anterior lobe of the cerebellum.

The possibility that the postural afferent systems may be modified by cortico-cerebellar impulses has been suggested. It is uncertain whether the forced postures and movements observed during the first weeks in the experimental animals are indicative of vestibular release or merely related to the operative procedures adjacent to the eighth nerve and vestibular nuclei. It is significant that these postural manifestations were much more enduring than obvious neighborhood symptoms referable to the V and VII nerves. There was no microscopic evidence of injury to the vestibular system.

The relation of the present experimental results to previous theories concerning the functional anatomy of the cortico-ponto-cerebellar system requires brief consideration. No interference with the proper execution of motor formulae (Tilney and Riley 1921) was observable after lesions of this system. Similarly no deficits in the capacities for precise manual function of the forelimbs, nor any lack in learned versus phylogenetically conditioned behavior (Tilney 1928; Yochelson 1936) could be noted. Indeed, if interference with the execution of learned motor formulae were to be brought about by severing the cortico-ponto-cerebellar pathways, it should certainly show up in animals trained in the problem box techniques, for the work of

* Data indicating progressive widespread atrophy of Purkinje cells after lesions to the brachia pontis will be reported in a later paper.

Jacobsen (1931) indicates that these patterns are a function of the areas of the cerebral cortex from which a preponderant number of the cortico-pontine fibres arise. At no time did any of the animals display states even remotely resembling decerebrate rigidity (Wilson 1920; Warner and Olmstead 1923; Smith 1924; Abbie 1934), nor was there at any time a post-operative condition which appeared as an "akinetic-hypertonic" syndrome (Jakob 1923). Save for slight transient post-operative dysmetria, there were no immediate signs suggesting symptomatology of a more classical cerebellar nature.

It is worth mentioning again that close observation of the terminal incoördination of gait seen in the bilaterally operated animals indicated that the fault lay in *inadequate coördination of the lower with the upper extremities in locomotion*, and that this incoördination bore only a superficial resemblance to a true "cerebellar ataxic gait." The following statement of Walshe (1927) concerning cerebellar phenomena is pertinent: "On the other hand, a disturbance of the cortical process of motor synthesis. . . may well underlie cerebellar ataxia . . . The disorder of some higher grade of coördination involving the participation of the cerebral motor cortex and concerned with the harmonious relationship between component coördinated units of large voluntary movement complexes may conceivably be the basis of the cerebellar symptom complex." This concept of the cortical motor areas as the site of genesis of cerebellar phenomena has been verified by the experiments of Fulton, Liddell and Rioch (1932) and by those of Aring and Fulton (1936).

Summary and Conclusions

The effects of section of the brachium pontis were studied in three monkeys (2 mangabeys, 1 Java monkey) over periods of 5 to 20 months. The observations included psychobiological tests (problem boxes) to which the animals were previously trained, determinations of cerebellar functions, posture, gait, equilibrium, muscle tone, and personality characteristics. The operative lesions and their resultant degenerations were verified histologically. The results may be summarised as follows:

1. Neither the retention nor the execution of learned behavior problems was significantly affected by unilateral or bilateral section of the brachium pontis.

2. Unilateral section of the brachium pontis was followed by curvature of the head and spine, spiralling and circus movements toward the side of the lesion; awkwardness of the lower extremities in locomotion, with incoördination between the hindlimbs and the forelimbs; slight hypotonia of both lower extremities. These symptoms disappeared within three to four weeks. A decrement in activity sometimes endured for a somewhat longer time. Transient dysmetria and nystagmus were present for a few days after operation. No tremors in either voluntary or associated movements were noted at any time.

3. Bilateral section of brachium pontis resulted in the same symptoms as the unilateral operation, but enduring awkwardness of gait and diminished general activity were present. The hand-eye coördination was reduced 20 to 30 per cent below preoperative normal.

4. The bilateral operation was followed by a progressive symptom complex consisting of incoördination between the lower and the upper extremities in locomotion, dysequilibrium, and sluggishness of general behavior.

The following implications may be drawn from the results of this study:

1. The cortico-ponto-cerebellar system is not necessary for the performance of precise manual functions or learned behavior.

2. The complete compensation which occurs following unilateral lesions indicates that the cortico-ponto-cerebellar system is capable of bilateral function.

3. Functionally the cortico-ponto-cerebellar system seems to be necessary for the coördinated activity of large movement complexes, such as the relationship between the lower and the upper extremities in locomotion.

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